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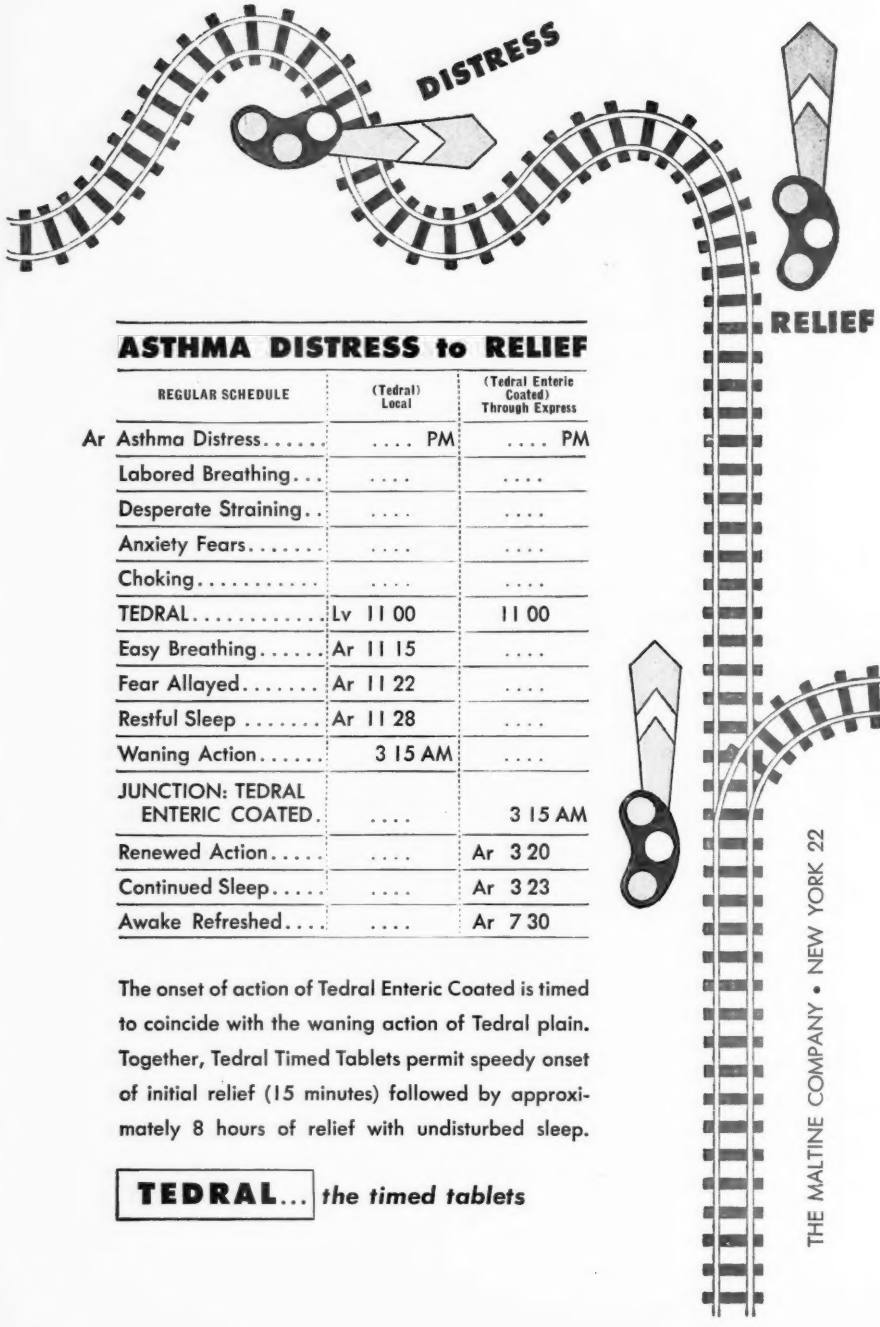

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ANNALS of ALLERGY

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IMMUNITY TO DIPHTHERIA INDUCED BY A BOOSTER DOSE OF DIPHTHERIA TOXOID PURIFIED BY ABSORPTION AND ELUTION

Based on a Study of Fifty-five Allergic Children

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New York, N. Y.

DESPITE the numerous investigations conducted over a period of years to purify diphtheria toxin and toxoid, including experiments in absorption with calcium phosphate,[1-7,11-13] detoxified crude bacterial filtrates and alum-precipitated toxoids are still mainly used in prophylaxis against diphtheria. As a consequence, frequently disturbing undesirable systematic reactions occur, especially after the administration of a booster dose of toxoid to older children. It becomes obvious, therefore, to replace the toxoids used now with preparations capable of causing minimal undesirable local and systemic reactions.

Crude toxoid prepared by detoxification of bacterial filtrates with formalin, in addition to proteins of true exotoxin, contains somatic antigens, i.e., soluble substances of proteinic nature that form precipitins with antibacterial serum. The biological significance of these substances and methods of their separation from the toxin have been described fully by Parfentjev, Waldschmidt and Weil.[9] It was shown that under controlled conditions selective absorption of somatic antigens with magnesium hydroxide can be achieved. This absorption, however, resulted in very little reduction of the total nitrogen content in the toxin. In a later work, Parfentjev and Goodline[8] described the methods of purification of toxoid prepared from absorbed toxin. By these methods they were able to eliminate more than 90 per cent of the original nitrogen. Purified toxoid was prepared from absorbed toxin by the subsequent steps of detoxification with formaldehyde, dialysis, absorption of the

From the Children's Allergy Clinic, The Mount Sinai Hospital, New York.
Dr. I. A. Parfentjev, of the Lederle Laboratories, gave technical assistance in this study.
The preparations of calcium phosphate diphtheria toxoid and eluted diphtheria toxoid used in this study were furnished by Lederle Laboratories, Pearl River, New York.
Presented at the third annual meeting of the American College of Allergists at Atlantic City, New Jersey, June, 1947.

TABLE I. DIPHTHERIA ANTITOXIN TITERS OF FIFTY-FIVE ALLERGIC CHILDREN OBTAINED AFTER THE BOOSTER INJECTIONS OF CALCIUM PHOSPHATED OR ELUTED DIPHTHERIAL TOXOIDS

Antitoxin Titer, Units per c.c. of Serum Before and After Injection of Toxoid									
Case Number	Before Booster Dose	After Booster Dose of 1 C.C.			Case Number	Before Booster Dose	After Booster Dose of 0.5 C.C.		
		Week	Months				Week	Months	
		1	1	2			1	1	2
Calcium Phosphated Diphtherial Toxoid									
1.	>0.02 <0.04	0.1	0.1	>0.02 <0.04	19.	0.1	0.2	2.0	2.0
2.	0.2	>4.0 <6.0	4.0	>3.0 <6.0	20.	0.1	1.0	>0.2 <0.5	>0.2 <0.5
3.	>0.2 <0.5	>0.5 <1.0	2.0	>2.0 <4.0	21.	0.1		>2.0 <4.0	>2.0 <4.0
4.	>0.2 <0.5	>2.0 <4.0	6.0	10.0	22.	>0.1 <2.0	6.0	6.0	8.0
5.	>0.2 <0.5	>2.0 <4.0	>6.0 <12.0	16.0	23.	0.2	4.0	6.0	>3.0 <6.0
6.	>0.2 <0.5	4.0	12.0	12.0	24.	>0.2 <0.5	2.0	>4.0 <8.0	8.0
7.	0.5	>8.0 <10.0	14.0	>12.0 <24.0	25.	0.5	2.0	8.0	>7.0 <14.0
8.	>0.5 <1.0	2.0	4.0	3.0	26.	0.5	>6.0 <8.0	>5.0 <10.0	10.0
9.	>0.5 <1.0	>6.0 <8.0	>5.0 <10.0	10.0	27.	0.5	8.0	7.0	>6.0 <8.0
10.	>0.5 <1.0	8.0	12.0	20.0	28.	0.5	12.0	>10.0 <20.0	20.0
11.	1.0	6.0	10.0	10.0	29.	1.0	4.0	12.0	>10.0 <20.0
12.	1.0	20.0	>30.0 <60.0	30.0	30.	1.0	4.0	>12.0 <15.0	>10.0 <20.0
13.	>1.0 <2.0	2.0	8.0	>4.0 <8.0	31.	1.0	6.0	6.0	16.0
14.	>1.0 <2.0	4.0	6.0	12.0	32.	>1.0 <2.0	4.0	6.0	>6.0 <12.0
15.	>1.0 <2.0	>4.0 <6.0	>8.0 <16.0	16.0	33.	>1.0 <2.0	>6.0 <8.0	12.0	>3.0 <6.0
16.	2.0	6.0	20.0	20.0	34.	2.0	4.0	6.0	5.0
17.	2.0	12.0	12.0	14.0	35.	2.0	8.0	14.0	14.0
18.	4.0	6.0	>10.0 <20.0	20.0	36.	>3.0 <4.0	>4.0 <6.0	>3.0 <6.0	>3.0 <6.0
Eluted Diphtherial Toxoid									
37.	0.002		0.02	0.1	46.	0.01	0.2	>2.0 <4.0	
38.	>0.1 <0.5	>8.0 <16.0		>8.0 <16.0	47.	>0.01 <0.04	2.0	8.0	14.0
39.	0.5		>4.0 <6.0	8.0	48.	>0.01 <0.04	4.0	4.0	4.0
40.	>0.5 <1.0	2.0	>8.0 <16.0	20.0	49.	>0.1 <0.5	>0.1 <0.5	1.0	>8.0 <16.0
41.	>0.5 <1.0		>30.0 <60.0	>30.0 <60.0	50.	>0.1 <0.5	>2.0 <4.0	8.0	>6.0 <12.0
42.	1.0	>2.0 <4.0	6.0	12.0	51.	>0.1 <0.5	>3.0 <4.0	>4.0 <8.0	12.0
43.	1.0	>8.0 <16.0	16.0	15.0	52.	>0.5 <1.0	8.0	32.0	>50.0 <100.0
44.	>1.0 <2.0	16.0	16.0	>10.0 <20.0	53.	>0.5 <1.0	20.0	>8.0 <16.0	>12.0 <24.0
45.	2.0	>16.0 <32.0	>15.0 <30.0	>15.0 <30.0	54.	>2.0 <4.0	>8.0 <16.0	>16.0 <32.0	32.0
					55.	>4.0 <8.0	>10.0 <20.0	>20.0 <40.0	40.0

toxoid with calcium phosphate, and finally, elution of the purified toxoid. This method yields a highly purified product which contained very little nitrogen (250 Lf per c.c.), was free from bacillary proteins, and remained highly antigenic. Injections of this purified diphtherial toxoid into animals has shown its antigenic properties to be unimpaired.

In this communication fifty-five allergic children with bronchial asthma or hay fever or both were selected for injection with these purified diphtherial toxoids. All of these children had been previously immunized with combined diphtheria and tetanus toxoids, alum-precipitated[10]. Their average age was fourteen and one half years. The purpose of this investigation was to determine (1) the incidence of local and systemic reactions in allergic children following a booster dose of highly purified diphtherial toxoids in an age group of children in whom unfavorable reactions following a booster dose of crude diphtherial toxoid occurs most frequently, (2) the time of maximum antitoxin response, and (3) the incidence of positive cutaneous tests to the purified and crude diphtherial toxoids.

MATERIALS AND METHODS

The total number of samples of blood titrated for diphtheria antitoxin from the thirty-six allergic children injected with the booster dose of calcium phosphated toxoid was 143. The total number of titrations from nineteen allergic children given the booster injection of eluted diphtheria toxoid was seventy-one. A grand total of 214 samples of blood had been titrated after the booster injections. The dose consisted of 0.5 c.c. or 1 c.c. of the calcium phosphated toxoid or the eluted toxoid, injected subcutaneously.

TIME OF OCCURRENCE OF MAXIMUM RESPONSE TO THE TOXOID PREPARATIONS

A review of Table I shows the calcium phosphated and eluted diphtherial toxoids to possess marked antigenic potency, a booster dose of either toxoid causing the levels to rise as high as 40 units of antitoxin per cubic centimeter of blood. Moreover, there is no appreciable difference in the antitoxin response after a booster injection of 0.5 c.c. or 1 c.c. of either toxoid preparation. For this reason there will be no segregation of the maximum antitoxin values obtained.

To determine the maximum antitoxin response following a booster toxoid, two or more tests were done on fifty-five patients within two months after the injection. The maximum antitoxin response occurred after one week in ten children, after one month in twenty children, and after two months in twenty-five children.

REACTIONS AND SENSITIVITY

Calcium phosphated toxoids.—Fourteen children subcutaneously injected with 1 c.c. of the toxoid were available for study. Seven children

had severe, hot and painful local reactions lasting up to four days. In four of these seven children the swelling was about the size of a small orange, and in the other three children the swelling involved the entire arm. On the seventh day the swelling became moderate and indurated, which progressively grew smaller and by the sixteenth day was about gone. Three of these children had an elevation of temperature up to 101.5° F. lasting one day. One of these patients also had a severe headache.

Five patients had only a moderate local reaction for from one to four days with some pain at the site of the reaction.

One patient had only a slight local reaction and another patient had none.

Another group of sixteen children injected with 0.5 c.c. of the calcium phosphated toxoid were available for study. Nine children had a severe local reaction lasting for three days. The induration cleared in two weeks. In one of the nine children the swelling involved the entire arm. Two of these nine children had an elevation of temperature to 100.8° F. for one day, and a third child had a temperature of 102° F. for two days with urticaria. The latter child had been previously cleared of hives which was caused by contact with wool.

Six children had moderate local reactions and two of these children also had malaise and anorexia for one day after the injection of toxoid. The reactions were painful for several days in three of these six children.

The remaining patient had only a slight local reaction.

Calcium phosphated and eluted toxoid.—Six patients injected with 1 c.c. of the toxoid were available for report. Three of these patients had severe local reactions for three days with malaise and anorexia for one day.

Two patients had moderate local reactions for a few days and another patient had no local reaction.

None of the patients in this group had an elevation of temperature following the injection of the toxoid.

Another group of seven patients injected with 0.5 c.c. of eluted toxoid were available for study. Only one patient had a severe local reaction, the swelling involving the entire arm for five days. He also had a temperature up to 104° F. for three days. Chills started twelve hours after the injection.

Two patients had a moderate local reaction, another one a slight local reaction, and the remaining three patients had no local reaction. None of the patients in this group had an elevation of temperature after the injection.

Despite the elimination of over 90 per cent of the nitrogen in the preparations employed, the occurrence of severe local reactions following a booster dose associated with elevation of temperature occurred

frequently enough with the calcium phosphated toxoid to preclude its use in the immunization of children against diphtheria. The eluted calcium phosphated toxoid may be employed for immunization since the incidence of reactions following booster doses, especially the febrile type in older children, is less than that experienced by another comparable group of children injected with combined diphtheria and tetanus toxoids, alum-precipitated.[10]

Comparative intradermal tests with 1 to 100 dilution of crude yellow diphtherial toxoid and eluted calcium phosphated toxoid in 113 allergic children from eight to fifteen years of age (all of whom had received immunization against diphtheria in early childhood and many of whom had had subsequent booster doses) showed positive delayed reactions with the yellow toxoid in twelve children, four of whom also reacted positively to the eluted toxoid. Another ten children reacted to both the crude and eluted toxoids but the reactions to the eluted toxoids were definitely smaller than those with the yellow toxoid. No child who was negative to the eluted toxoid reacted positively to the yellow toxoid.

From this it appears that despite the technical advantages of the eluted toxoids over the crude yellow toxoid, children still react by the test to the eluted preparation, though much less frequently and less intensely than with the yellow toxoid.

In view of the above findings, the eluted calcium phosphated toxoid can be regarded as a preparation pointing to definite progress in the search for a diphtherial toxoid capable of lowering the incidence of local febrile or systemic allergic reactions following its use.

SUMMARY

1. Fifty-five allergic children with bronchial asthma or hay fever or both were injected with purified diphtherial toxoids. Calcium phosphated toxoid was prepared from absorbed toxin by the subsequent steps of detoxification with formaldehyde, dialysis, absorption of the toxoid with calcium phosphate, and eluted toxoid was prepared by the elution of the purified calcium phosphated toxoid.

2. These purified diphtherial toxoids equally possess marked antigenic potency. There was no appreciable difference in the antitoxin response after an injection of 0.5 c.c. or 1 c.c. of either toxoid preparation.

3. The maximum antitoxin response for the majority of children with each toxoid preparation occurred from one to two months after injection.

4. Despite the elimination of over 90 per cent of the nitrogen in the preparations employed, severe local and systemic reactions occurred sufficiently often following the injection of the calcium phosphated toxoid to preclude its use in the immunization of children against diphtheria. However, the eluted calcium phosphated toxoid may be employed for immunization with advantage, since the incidence of reactions following injections, especially the febrile type in older children, is less than that

experienced by another comparable group of children injected with alum-precipitated toxoid.

5. Comparative intradermal tests with 1:100 dilution of crude yellow diphtherial toxoid and eluted calcium phosphated toxoid showed the latter preparation to give a decidedly lower incidence of positive reactions.

6. The eluted calcium phosphated diphtherial toxoid can be regarded as a preparation pointing to definite progress in the search for diphtherial toxoid capable of lowering the incidence of local, febrile or systemic allergic reactions following its use in allergic children.

REFERENCES

1. Abt, G.: Sur la purification de la toxine diphtherique au moyen des precipitates de phosphates de chaux. Ann. inst. Pasteur, 42:1336-1365, 1928.
2. Ando, K., and Komiyama, T.: Factors influencing the speed of flocculation. J. Immunol., 28:331-343, 1935.
3. Eaton, M.D.: The purification and concentration of diphtheria toxin. I. Evaluation of previous methods; description of a new procedure. J. Bact., 31:347-366, 1936.
4. Eaton, M.D.: The purification and concentration of diphtheria toxin. II. Observations on the nature of the toxin. J. Bact. 31:367-383, 1936.
5. Miller, F. A.; DeVries, T., and Miller, M. A.: Absorption of diphtheria toxin and toxoid on colloidal gels. Proc. Indiana Acad. Sci., 44:88-92, 1934.
6. Ohyama, Seiichi: Sur la purification de la toxine diphtherique. J. Biochem. Japan, 13:255-272, 1934.
7. Pappenheimer, A.M., Jr.: Diphtheria toxin. I. Isolation and characterization of a toxin protein from Corynebacterium diphtheriae filtrates. J. Biol. Chem., 120:543-553, 1937.
8. Parfentjev, I.A., and Goodline, M.A.: Diphtherial toxoid purified by absorption. J. Bact., 50:661-666, 1945.
9. Parfentjev, I.A.; Waldschmidt, A., and Weil, A.J.: Absorption of bacterial antigen from diphtheric toxin and toxoid by magnesium hydroxide. J. Immunol., 44:325-328, 1942.
10. Peshkin, M.M.: Immunity to tetanus induced by a third dose of toxoid three months to four years after basic immunization. Based on a study of 159 allergic children. J. Mt. Sinai Hospital, 12:555-556, 1945.
11. Roux, E., and Yersin, A.: Contribution a l'etude de la diphtherie. Ann. inst. Pasteur, 3:273, 1889.
12. Wadsworth, A.; Quigley, J. J., and Sickles, G. R.: The preparation of diphtheria toxoid absorbed on calcium phosphate. J. Bact., 29:44-45, 1935.
13. Wadsworth, A.; Quigley, J.J., and Sickles, G.R.: Preparation of diphtheria toxoid. The action of formaldehyde precipitation by calcium. J. Infectious Dis., 61:237-250, 1937.

All periodical publications of the British Medical Association are now obtainable through Grune & Stratton, Medical Publishers, 381 Fourth Avenue, New York 16, New York, who have been appointed by the Association sole agents for the United States beginning with January, 1948.

The journals are: *British Medical Journal,* published weekly, $14 a year; *Abstracts of World Medicine,* published monthly, $13 a year; *Abstracts of World Surgery, Obstetrics and Gynecology,* published monthly, $9 a year.

Quarterly journals obtainable at the uniform subscription rate of $5.50 a year are: *Annals of the Rheumatic Diseases, Archives of Disease in Childhood, British Heart Journal, British Journal of Industrial Medicine, British Journal of Pharmacology and Chemotherapy, British Journal of Social Medicine, British Journal of Venereal Diseases, Journal of Clinical Pathology, Journal of Neurology, Neurosurgery and Psychiatry, and Thorax.*

BRONCHIAL ASTHMA IN PATIENTS OVER THE AGE OF FIFTY-FIVE YEARS

Diagnosis and Treatment

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BRONCHIAL asthma occurring after the age of fifty-five years is, in our experience, usually due with about equal frequency to food and inhalant allergy, rarely to drug allergy, and very rarely to bacterial allergy. This opinion is based on the demonstrated causes in 173 private patients who obtained excellent or good results from our treatment. To judge the results of our present therapy, only those patients seen during the last six years who co-operated for at least six months are considered. During this period 1,061 other private patients with ages from one to fifty-five years, suffering with bronchial asthma from similar causes, have obtained such results.

TABLE I. OCCURRENCE AND DURATION OF BRONCHIAL ASTHMA IN 173 PATIENTS OVER THE AGE OF FIFTY-FIVE YEARS
Successfully treated from 1940 to 1946

Males	98; Females 75
Onset of Asthma after 55 years	51 patients
Onset of Asthma between 50 and 55 years	21 patients
Duration of Bronchial Asthma	
0—1 year	22 patients
1—2 years	22 patients
2—5 years	39 patients
5—10 years	36 patients
10—20 years	16 patients
Over 20 years	38 patients
Perennial Asthma	129 patients
Recurrent Exaggerations or Attacks	80 patients
Seasonal Exaggeration:	
In Summer	30 patients
In Fall	42 patients
In Winter	55 patients
In Spring	47 patients

The number of males and females, the duration of the asthma, the frequency of perennial asthma, of recurrent attacks, and seasonal exaggeration of the symptoms are shown in Table I. Exaggeration in the fall, winter and spring months suggested that indoor inhalants and especially food allergy[9] might be responsible.

The frequency of other manifestations of allergy, especially perennial and seasonal nasal allergy, is shown in Table II. A history suggestive but not necessarily diagnostic of food allergy occurred in seventy-eight of the 173 patients. Such a history suggests but does not necessarily indicate clinical food allergy. The familiar predisposition to bronchial asthma in contrast to other manifestations of allergy is shown in Table III.

DETERMINATION OF THE ALLERGENIC CAUSES

History.—A detailed, well-taken history often indicates probable food, pollen or other inhalant allergies and justifies treatment based on such conclusions.

TABLE II. OTHER MANIFESTATIONS OF ALLERGY

Perennial Nasal Allergy	97 patients
Seasonal Nasal Allergy (In the Spring, Summer and Fall)	33 patients
Urticaria	15 patients
Eczema	17 patients
Gastrointestinal Symptoms	41 patients
Recurrent Headaches	24 patients
Dietary History—Positive	78 patients
Drug History—Positive	14 patients
Environmental History—Positive	39 patients

TABLE III. FAMILY HISTORY OF CLINICAL ALLERGY

Bronchial Asthma	81 patients
Nasal Allergy	18 patients
Recurrent Headaches	15 patients
Gastrointestinal Symptoms	6 patients
Urticaria	2 patients
Eczema	5 patients

The writers' plan for history taking is published elsewhere.[5,6,7] A dietary history is most important, based on questions about single foods, such as "Do you drink and like milk?", "Do you eat and like eggs?", et cetera. The drug history should include all reactions to drugs or medicaments. The environmental history should record all home, occupational and recreational sources of inhalants which might cause asthma.

Skin Testing.—The results of skin testing of these 173 patients in Table IV showed that reactions of varying degrees occurred in these elderly patients as in younger groups.[11] Skin testing was done by the scratch method. Intradermal testing with inhalant allergens which failed to react by the scratch method was also done in selected patients. Positive skin reactions usually occurred to inhalants and infrequently to foods responsible for the asthma. Positive reactions, moreover, were not always associated with clinical allergy, especially to causative foods.[8,14]

No skin reactions occurred in seventy-three of the 173 patients. Of these seventy-three patients, fifty-eight were allergic only to foods, eleven to pollens and foods and four to pollens alone. Thus, the fallibility of the skin test in the determination of food allergy and, to a lesser extent, inhalant allergy is demonstrated.

Because of the writers' experience that many intradermal tests with foods are not specific or indicative of past or potential allergy,[8] such testing is not routine.

The Study and Control of Food Allergy.—Because of this fallibility of the skin test in the determination of food allergy, we have used the senior

TABLE IV. NUMBER OF PATIENTS WHO REACTED TO INDIVIDUAL ALLERGENS IN VARIOUS GROUPS BY THE SCRATCH TEST

Degree of Reaction	0 — 1+	2 — 5+	6 — 10+	Total Patients
Grass	22	33	7	62
Fall	17	23	13	53
Tree	23	22	5	50
Flowers	15	28	2	45
Animal Emanations	13	26	1	40
Miscellaneous Inhalants	24	15	1	40
House Dust	19	20	0	39
Fungi	8	10	0	18
Food	13	17	1	31

Seventy-three patients gave no skin reactions to any food or inhalant allergens.

writer's elimination diets[7] to study suspected food sensitization. For fifteen years the cereal-free elimination diet has been preferred because of the frequency of allergy to the cereal grains (one or more) as well as to milk, egg, wheat, chocolate and other foods excluded from the diet. These diets are modified when there is evidence of allergy to included foods.

The advantages of the standardized elimination diets are that the patient is given (1) a specific list of allowed foods, (2) detailed menus, (3) specified amounts of foods which will maintain or increase weight, (4) tested recipes for bakery products, (5) proper amounts of calcium and specified vitamins, and (6) directions for eating away from home to prevent errors in the diet.

Good results require (1) absolute adherence to the diet, (2) frequent conferences with the doctor who must detect errors, either willful or unintentional, and (3) realization that relief will appear in two to fourteen days, depending on the time the allergens of formerly eaten foods remain in the body and the time required for the cells of the lungs to recover from the allergenic reactions.

The prolonged use of the elimination diets in these patients caused a gain of weight in sixty, no change in sixty-seven, desired loss of weight in twenty and undesired loss, moderate in degree, in only ten patients.

The Study and Control of Inhalant Energy.—Properly taken histories often indicate pollen, animal emanation, dust, fungus or other inhalant allergy. Skin tests to the causative inhalants at times are negative, though much less often than to allergenic foods. Positive reactions, moreover, may not be associated with clinical allergy.

Environmental control and pollen filters when indicated are beneficial. Desensitization usually is necessary to all suspected inhalants impossible to exclude from the patient's environment. This treatment usually requires successively stronger dilutions up to the 1:500 or the 1:50 dilution for satisfactory results. Co-seasonal therapy, however, requires very weak dilutions, such as a 1:5,000,000 or 1:5,000,000,000 or weaker.

Prolonged desensitization for months or for one or more years usually is necessary.

Allergy to fungi is not common in California and the Southwest.

TABLE V. CAUSES OF BRONCHIAL ASTHMA DETERMINED BY GOOD RESULTS FROM SPECIFIC CONTROL

Food and Other Allergies	142 patients
Food Allergy Alone	70 patients
Inhalant and Other Allergies	114 patients
Inhalant Allergies Alone (Other than Pollen)	15 patients
Pollen and Other Allergies	**98 patients**
Pollen Allergies Alone	16 patients
Animal Emanations and Other Allergies	24 patients
Miscellaneous Inhalant and Other Allergies	28 patients
House Dust and Other Allergies	**35 patients**
Fungus and Other Allergies	? patients
Bacterial and Other Allergies	5 patients

Bacterial Allergy.—In this series bacterial allergy was a major cause in no patient. It was of probable secondary importance to food and/or inhalant allergies in five patients. The fact that our good and excellent results were obtained in these 173 patients with no operations on the nose or sinuses except for the removal of polyps in three speaks especially against bacterial allergy as a cause. The writers agree with Rackeman,[3] Tuft[13] and others that hyperplasia, polyps and other changes in the nose and sinuses are due to allergy and not infection. Severe vascular allergy did not occur in any patient.[2,4]

Physical Examinations and Laboratory Studies.—Routine physical, blood and urine examinations, Kline tests and roentgen ray studies of the lungs and, when indicated, of the sinuses were made on all patients. The many, non-allergic causes of wheezing, cough and dyspnea, especially cardiovascular disease, were always in mind.

CAUSES OF BRONCHIAL ASTHMA IN 173 PATIENTS OVER THE AGE OF FIFTY-FIVE YEARS WITH GOOD OR EXCELLENT RESULTS

To obtain these results, the allergies indicated in Table V were controlled. Excellent results mean complete freedom from symptoms or only slight occasional wheezing or coughing, except with failure to adhere to the necessary diet, environmental control or desensitization therapy. Good results mean relief from symptoms, except for occasional wheezing or coughing with exertion or at times during the night.

The frequency of food allergy as the sole cause and especially in association with inhalant allergies is shown in the table. Inhalants alone were responsible about half as often as were foods. In association with foods, they caused asthma a little less frequently than did foods in association with inhalants. The frequency of pollens, animal emanations and other inhalants is shown in the table.

Patients of Over Fifty-five years Who Were Unrelieved of Bronchial Asthma.—During this six-year period, sixty-two additional patients over fifty-five years were seen. As shown in Table VI, co-operation was satisfactory in only seven and in four of these the period of co-operation was less than six months. Death occurred in one patient from spontaneous pneumothorax in eighteen hours after treatment was started.

TABLE VI. UNRELIEVED BRONCHIAL ASTHMA IN SIXTY-TWO PATIENTS OVER FIFTY-FIVE YEARS OF AGE SEEN SINCE 1940

Good Co-operation	7 patients
Poor Co-operation	55 patients
Time of Treatment:	
None	25 patients
1 to 4 weeks	17 patients
1 to 3 months	13 patients
3 to 6 months	4 patients
6 to 12 months	3 patients

TREATMENT OF BRONCHIAL ASTHMA

Specific Control.—

1. When seasonal pollen, specific inhalant or drug allergies are not the sole obvious causes, food allergy is studied immediately with the senior writer's standardized cereal-free elimination diet.[7]
2. When inhalant allergy is indicated by history or skin testing, strict environmental control and, when necessary, desensitization with all allergens the patient continues to inhale are necessary.
3. Rare bacterial allergy, especially in teeth and less often in other foci, requires removal of such foci and, at times, careful desensitization with autogenous vaccine.
4. Allergy to drugs, especially to aspirin, must be remembered.

Symptomatic Control.—This is necessary until the above specific measures reduce or eliminate the symptoms.

1. Ephedrine by mouth with or without small doses of barbital.
2. Aminophyllin, 3 to 6 grains by mouth, every six hours if necessary.
3. Potassium or sodium iodide, 5 to 20 drops of the saturated solution in water, two to four times a day. Allergy to iodine is indicated by swelling of the submaxillary glands, coryza, or nasal blocking, headaches or skin eruption.
4. Pyribenzamine or Benadryl by mouth.
5. Epinephrine 1:100 by inhalation.
6. Epinephrine 1:1000 subcutaneously, 0.3 c.c. to 0.8 c.c. every two hours if required.
7. Epinephrine in gelatin intramuscularly for a more prolonged effect.[12]
8. Aminophyllin, 3.5 to 7.5 grains by vein during a three- to five-minute period every eight hours if necessary for severe symptoms.
9. Morphine or other opiates, demerol, paraldehyde, chloral or barbitals are absolutely contraindicated, in our experience. Depression of the

respiratory center may lead to anoxemia and, at times, death. Atropin also is contraindicated.

10. When symptoms persist, roentgen ray therapy of the lungs or fever therapy may be tried with questionable benefit. Anesthesia, especially with ether in oil, is no longer advised. Bronchoscopy is only justifiable when bronchial obstruction from foreign bodies, tumors or large plugs of mucus is probable.

11. Antibiotic drugs are indicated for complicating infections of the lungs or other tissues.

12. Though reassurance has been routine, prolonged psychotherapy has not been used in any patient.

TREATMENT OF INTRACTABLE BRONCHIAL ASTHMA

Specific Control.—

1. These patients require hospitalization or comparable care at home. Immediate consideration of possible food, inhalant or rare bacterial allergy is imperative. Unless inhalants are the obvious sole cause, food allergy immediately is studied with the cereal-free elimination diet. Vomiting requires intravenous glucose in saline or water, according to fluid and salt requirements. Severe asthma may necessitate the elimination diet in liquid, soft, minced or pureed form, containing adequate calories. If food allergy is the cause, improvement may not be obvious for five to fourteen days. With improvement, the regular published menus should be used.

2. Inhalant allergy requires strict environmental control. Pillows and mattresses must be encased in dustproof covers. If pollen is suspected, a window filter is advisable. Desensitization should be started only after definite improvement occurs.

3. Bacterial and drug allergies need study as advised in moderate bronchial asthma.

Symptomatic Control.—

1. Epinephrine 1:1000 subcutaneously in doses of 0.5 c.c. to 0.85 c.c. every two hours may give relief.

2. If epinephrine is not effective, aminophyllin by vein in 5 to 7.5 grain doses every eight hours is indicated.

3. With dehydration, intravenous 5 per cent glucose in saline and water should be given.

4. For extreme dyspnea and especially cyanosis, oxygen by a BLB mask or tent is necessary.

5. As in moderate bronchial asthma, all sedatives are contraindicated.

6. With relief, measures for the control of moderate bronchial asthma described above will be effective.

CASE REPORTS

Case 1.—A woman, Mrs. C. P., aged sixty-six, was first seen on October 3, 1941, because of bronchial asthma since 1937. It started in December with moderate symp-

toms. Wheezing and coughing continued, and in the late spring she went to New Mexico and Colorado, where relief occurred. Desensitization to molds was given. She returned to Indiana in September, and in October "when the furnaces were started," asthma returned and continued until early summer. Asthma returned in October and continued in spite of treatment. Being advised to move to an area free of smoke and dust in the winters, she came to Berkeley in 1940. Since then asthma has been absent, or very mild in the summers, returning in early October and continuing until the spring last year and being severe in the last three weeks.

She gave no history of any other manifestations of allergy. A "winter cough" had been present for five years before her asthma developed.

She knew that milk had caused asthma for three years, and she suspected meat, fish, various vegetables, citrus fruits and watermelon. Aspirin caused itching of the hands and feet, and quinine caused nervousness. Smoke and dust were suspected as causes of the asthma.

Her maternal uncle had bronchial asthma.

Her physical examination was negative except for diffuse evidences of bronchial asthma in her lungs. Her blood pressure was 150/90. Her blood and urine analyses were normal. The roentgen-ray of her lungs showed moderate emphysema.

Skin testing with all important foods gave no reactions. Skin testing with all important inhalants gave 1-plus and 2-plus reactions to several fall pollens and goose feathers.

Treatment and Progress.—She was placed on the writer's cereal-free elimination diet and given 12 drops of saturated solution of potassium iodide three times daily. In three days, she reported great relief and undisturbed sleep. In two weeks, she was so well she motored by way of the Southwest to Indiana to her son's wedding, returning to Berkeley in December. In Indiana she remained on her elimination diet all the time. No asthma occurred even though the furnaces were on, and she slept in bedrooms in which environmental control was absent.

Since then no asthma has occurred except when she has taken milk, egg, fish or wheat from September to May. In the summer months if moderate amounts of these foods are eaten, slight occasional asthma occurs.

Comment.—Food allergy was the sole cause of this patient's bronchial asthma which first developed at the age of sixty-two years. The winter cough for five previous years probably was the equivalent of the asthma. No previous clinical allergy had occurred in her life.

The negative skin reactions to the allergenic foods, and the absence of clinical allergy to the inhalants which gave positive reactions, illustrate the fallibility of the skin test in determining the causes of clinical allergy.

The activation of her bronchial asthma in October in Indiana, continuing through the winter to late spring, had been ascribed to "smoke from furnaces and dusts." The same activation, however, continued for two years in Berkeley where no coal or other smoke is in the air. The entire control of her asthma from fall to late spring for the last five years with the elimination diet shows that the activation of the asthma was due to the decreased tolerance for allergenic foods during the fall to late spring, which one of the writers has long reported in certain patients.[9] The absence of asthma in Indiana in December after being on the elimination diet for only one month, being in the same house where asthma had been severe in former Decembers, stresses the important role of food allergy in the production of her asthma.

Case 2.—A man, Mr. H. G., aged sixty-six, was first seen because of bronchial asthma in May, 1941. Coryza, lacrimation and itching of the eyes had occurred

five years before when threshing sugar beet seeds. Since then, in the winter months, nasal symptoms with a productive cough and a tightness in the chest had occurred. In June, 1940, these symptoms increased in degree, but were relieved in July and August. In the fall and winter, asthma persisted from sunset to sunrise and increased symptoms required hospitalization in February, March and May.

He gave no history of previous nasal or bronchial allergy or of any other manifestation of allergy. His dietary history revealed no idiosyncracies or dislikes for any foods. He lived on a ranch, but had no symptoms from inhalation of any tree, grass, weed or alfalfa pollens or any animal emanations or feed or grain dusts, rusts or smuts in the air.

Asthma had occurred in the mother and two maternal uncles.

Appendectomy in 1902 and polypectomy in 1940 had been done. His physical examination was negative except for diffuse evidences of bronchial asthma in the lungs and a blood pressure of 160/90. X-ray of the lungs showed moderate emphysema. His blood and urine analyses were normal except for an 8 per cent eosinophilia.

Skin testing with all important food and inhalant allergens by the scratch test was negative. Intradermal tests with inhalants gave 1-plus and 2-plus reactions to several of the grass and weed pollens and to dog and horse hair, silk, orris root, cottonseed and house dust allergens.

Treatment and Progress.—He was placed on the senior writer's cereal-free elimination diet and given 15 drops of saturated solution of potassium iodide three times daily and 1:100 epinephrine solution for inhalation. In two weeks his asthma had diminished and in two more weeks no attacks had occurred. His weight had increased from 162 pounds to 188 pounds.

Moderate nasal allergy continued, but no dust or pollen therapy was given. In two months his symptoms had disappeared and he was doing light ranch work. No asthma recurred, and in the summer of 1943 a general diet was resumed. In November asthma recurred and persisted until the cereal-free diet was resumed in late December. Since then rice, corn, and rye have been taken in the summer, but the strict diet, plus turkey, ham and all vegetables and fruits, has been followed each fall and winter. No asthma has been present. His recent weight is 192 pounds.

Comment.—The development of bronchial and nasal allergy at the age of sixty-one years without any previous evidence of allergy shows that hypersensitivity can arise in old age. The control of his asthma with the elimination diet without desensitization to any pollen or other inhalant to which his history and skin reaction indicated probable clinical allergy is of interest. The necessity of eliminating the cereal grains in winters and his tolerance of these during the summers illustrates the exaggeration of food allergy during the winter. The rapid gain of weight shows that nutrition and weight can be maintained with the writer's elimination diet.

Case 3.—A woman, Mrs. J. P., aged sixty, was first seen in February, 1944, because of bronchial asthma present for thirty years. She had been in Vallejo, California, for one year, having lived previously in British Columbia and in Kansas. Her asthma had always occurred in August, September and October. For the last eight months in Vallejo on the bay, asthma had continued every day and night.

Hay fever had recurred from August until the frosts for thirty years. Sneezing from dusts and soap powders also had occurred.

Recurrent headaches had been present for thirty years up to twelve years ago. Much distention, belching and constipation had occurred for fifteen years.

Her dietary history revealed the production of distention and gas in the colon from milk. At times all foods seemed to disagree. Her drug and environmental histories were negative from the allergic viewpoint.

In the family, the mother had had sick headaches, and one brother and two sisters had asthma.

Her physical examination was negative except for rhonchi, wheezing and râles throughout both lungs. Roentgen-ray of the lungs revealed moderate emphysema with depressed diaphragms. Her blood and urine analyses and her Kline test were negative.

Skin testing by the scratch method with all important inhalants showed a 3-plus reaction to feathers, 1-plus and 2-plus reactions to most of the grass pollens, 2-plus to 8-plus reactions to cocklebur and most of the chenopod, artemesia and ambrosia pollens, 2-plus to 5-plus reactions to chrysanthemum, cosmos and dahlia pollens and 1-plus to 2-plus reactions to acacia, oak, walnut and olive pollens. She also gave 2-plus reactions to stock house dust extracts.

Skin testing by the scratch method with all important foods gave no positive reactions.

Treatment and Results.—The writer's cereal-free elimination diet was ordered for the study of possible food allergy. In two weeks the asthma present for eight previous months was practically absent, and only one pillow was used at night.

Pollen therapy then was initiated with a 1:500,000 dilution of a multiple spring, summer and fall antigen. Moderate increase in the asthma occurred during the following eight weeks. With the reductions of the dose to the 1:50,000,000 dilution and the maintenance of the original diet, the asthma practically disappeared. In the next month it was found that 0.3 c.c. of this weaker dilution reproduced moderate asthma whereas 0.1 c.c. controlled the symptoms.

During the last two years 0.1 c.c. subcutaneously of the 1:50,000,000 dilution of the pollen antigen has been given the patient two times a week, and the cereal-free elimination diet, plus fish, all vegetables and fruits, has been continued. During the summer months rice, corn and rye have been eaten, but during the late fall and winter they have been excluded because of a cough and wheezing which gradually developed with their use. With the above treatment she was even free of asthma in Kansas in March, and only slight tightness in the chest occurred for two weeks in the fall of 1945 and none in 1946.

Comment.—The history of hay fever and asthma from August to November for thirty years in Kansas and for one fall in California, together with the large reactions to all types of pollen, stresses pollen as a major cause. In Kansas no clinical manifestations occurred from the grass and tree pollens which gave the reactions.

The writers' results from pollen therapy illustrate the value of the very dilute multiple antigens for the control of pollen allergy in some patients. The relief of her symptoms with 0.1 c.c. and not 0.3 c.c. of the 1:50,000,000 dilution illustrates similar experience in other patients.

Her asthma, present for the first time in the winter, was relieved in two weeks after the cereal-free elimination diet was given and before pollen therapy was started. This indicated food allergy as a cause. Since then it has been determined that cereal grains can be eaten in the summer without resultant asthma. During the winter months asthma has recurred unless the cereals have been removed from the elimination diet. This illustrates the writers' observations that food allergy is activated in some patients in maritime areas and during the fall to spring months.[10]

SUMMARY

1. Food and inhalant allergies with approximately equal frequency are the usual causes of bronchial asthma in patients over the age of fifty-five years, as they are in all other ages.

2. The recognition of the importance of food allergy has depended on the routine use of our standardized cereal-free elimination diet whenever food allergy was suspected. Clinical food allergy rarely could be demonstrated by skin testing.

3. The treatment of inhalant allergy has required strict environmental control when indicated and desensitization with inhalants which could not be excluded from the air of the patient's environment.

4. Though gradually increasing and final large doses of antigens usually were necessary for good results, some cases required extremely weak dilutions, especially during co-seasonal therapy.

5. The minimal evidence of infective asthma due to bacterial allergy and of unknown obscure intrinsic causes coincides with our experience in other ages.

6. The specific and symptomatic control of symptoms in moderate bronchial asthma and in intractable bronchial asthma is discussed.

7. Sedatives of all types are contraindicated since they depress respiration and at times result in death.

8. Antibiotics are required when a secondary bacterial infection is present.

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REFERENCES

1. Deamer, W. C., and Graham, H. W.: Respiratory mold allergy. A twelve months atmospheric survey in San Francisco. (To be published.)
2. Harkavy, J.: Vascular allergy. Pathogenesis of bronchial asthma with recurrent pulmonary infiltrations and eosinophilic polyseroritis. Arch. Int. Med., 67:709, 1941.
3. Rackemann, F. M., and Weille, F. L.: (a) Nasal sinusitis and asthma. A thesis. Arch. Otolaryngol., 30:1051, 39; (b) Intrinsic asthma. J. Allergy, 11:147, 1940.
4. Rackemann, F. M., and Greene, J. E.: Periarteritis nodosa and asthma, Ref. in J. Allergy, 11:15, 1940.
5. Rowe, A. H.: Bronchial asthma: its diagnosis and treatment. J.A.M.A., 3: 1827, 1938.
6. Rowe, A. H.: Bronchial asthma. In Nelson's Medicine, Chap. 7, 1938.
7. Rowe, A. H.: Elimination Diets and The Patient's Allergies. Second edition. Philadelphia: Lea and Febiger, 1944.
8. Rowe, A. H.: Evaluation of skin reaction in food sensitive patients. J. Allergy, 5:135, 1934.
9. Rowe, A. H.: Seasonal and geographic influences on food allergy. J. Allergy, 13:55, 1941.
10. Rowe, A. H.: Dermatitis of the hands due to atopic allergy to pollen. Arch. Dermat. & Syph., 53:437, 1946.
11. Rowe, A. H., and Rowe, A. Jr.: Bronchial Asthma in Infants and Children: Diagnosis and treatment (to be published).
12. Spain, W. C.; Strauss, M. D., and Fuchs, A. M.; A slowly absorbed gelatin-epinephrine mixture. J. Allergy, 10:209, 1939.
13. Tuft, L.: Bronchial asthma. A critical review. J. Allergy, 17:27, 1946.
14. Tuft, L.: Critical evaluation of skin tests in allergy diagnosis. J. Allergy, 14:355, 1943.

THE ALLERGENS OF MILL DUST
Asthma in Millers, Farmers, and Others

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AMONG all types of asthma which we consider to be occupational or connected with environment, asthma produced by inhalation of mill products, such as grains, dust, flour, and so on, has always been of special interest, as can be judged from the many papers published on this subject. The results are interesting because they explain asthma, not only in millers, but also in other workers who come in contact with the same products (laborers, bakers, and so forth) and even in people who have nothing to do with this work, since the allergens with which we are dealing, are conveyed by the air and can be of a more general importance, for example, the asthma epidemic described by Ancona,[7] due to the presence of *Tinea Granella* and *Pediculoides ventricosus* in the flour of a small village.

We have already published our own observations on this problem in successive papers,[14-17] and the aim of this article is to present a summary of our points of view.

It would be a mistake to uphold the concept that the cause of sensitization is always the same; the fact is, that in cereal or flour dust, and generally in the atmosphere of mills and factories and also in the air near by, in which a certain amount of dust from these establishments spreads, there can be found different elements, each of which can be the producer of sensitization in each case. This can be clearly seen when tests are made with intradermal injections using cereal extracts; in almost every person whose anamnesis would make us think of this sensitization, positive reactions can be seen; and in a high proportion of those cases with a positive intradermal reaction to cereal dust, passive transfer is positive with Prausnitz-Kustner's method. Some years ago, we gathered information in mills and factories and found that of 792 factory workers, thirty-six (4.5 per cent) had asthma and of 149 cases of millworkers, seventy-three (48.9 per cent) were asthmatic. Of all the cases of asthma which we were able to study well (fifty-two), a positive cereal-dust reaction was obtained in thirty-eight, and in 87.5 per cent of the tested cases (twenty-eight out of thirty-two), the Prausnitz-Kustner reaction was positive. The nature of the allergen, that for the time being remained obscure, was studied afterwards by us and other authors. We are now prepared to give the factors which can be taken as proven:

1. *Flour.*—Walker,[28] Grimm,[8] ourselves,[15] and others have shown the existence of real sensitization due to flour; in other papers,[15] we have

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reported asthma cases with positive intradermal and Prausnitz-Kustner reactions. Therefore, no doubt whatsoever remains. Some authors have studied asthma or spastic coryza in bakers (De Besche, Salen, and Juhlin-Denfelt,[22] Van Dishoeck and Roux,[25] and so forth).

However, flour sensitization, often through the digestive route, is one of the most frequent allergens in cases of complex, airborne allergy, which manifests itself by leukopenia shock, by pulse frequency (Coca[5]), or by our method of microprecipitin reactions.[1] Although sensitization of this type can be shown in some cases, it occurs more frequently with vegetables. In Spain, sensitization to carob beans *(Vitia monantha)* in farmers, is relatively common, and we have shown, not only clinically with intradermal and Prausnitz-Kustner passive transfer reactions, but also by experimental investigations, that the sensitizing allergen is the vegetable flour itself, or its proteins. Female guinea-pigs were sensitized with concentrated dust absorbed on alumina, according to the method of Friedman, and shock produced with different dust fractions by means of the Schultz-Dale phenomenon. Thus, the pure flour of this vegetable more likely than not provoked shock. With the exception of bakers, however, sensitization to flour is extremely uncommon in the handling of cereals, as the cause of the bad effects of cereal dust.

2. *Infestation by acarina (mites).*—Beginning with Ancona's discovery,[7] previously mentioned, others have studied the part that similar infestations might play. S. Van Leuwen and collaborators[26] found that flours were frequently infested by a mite *(Tyroglyphus farinae),* which they believed was the cause of its selective allergic effects. Almost at the same time, we studied sensitization by mites and found others, as well as the *Alaerobius,* that in our country frequently infest granaries and corn warehouses as *Glyciphagus* and *Tyroglyphus.* This infestation, which can reach crevices in furniture and may become a real plague (Von Ludwig[27]) in living quarters, was also shown in some of our cases, and was observed by others as well (Dekker,[9] et al.). In some cases, and to a limited extent in the particular case of granary asthma, we have shown specific sensitization by extracts of acarina, but in no case were we able to show passive transfer with the Prausnitz-Kustner method, which is in agreement with Grove's observations of a case of asthma caused by *Pediculoides.* In some cases it is possible, even in the absence of the passive transfer, sensitization due to this mite, but we were soon able to see from our studies that dust infested by it also contains fungi, and we become more and more convinced that these are the ones which really sensitize, owing to the small size of the spores and their great diffusibility.

3. *Fungus infections.*—Cadham,[3] in 1924, showed sensitization by *Puccinia Granella* in workers in wheatfields, and this is the first observation

TABLE I

Name	*Cereal reaction*	*Dust P-K*	*Tilletia reaction*	*Ustilago P-K*	*Pure reaction*	*Flour P-K*
M. Rod.	pos.		pos.		neg.	neg.
C. Pasc.	pos.	pos.	pos.	pos.	neg.	neg.
V. Rod.	pos.		pos.	pos.	neg.	neg.
E. Torr.	pos.		pos.		neg.	neg.
J. Trev.	pos.		pos.	pos.	neg.	neg.
G. Mat.	pos.	pos.	pos.	pos.	neg.	neg.
P. Klor.			pos.	pos.	neg.	neg.
A. Garc.	pos.		pos.		neg.	neg.
P. Sanch.	pos.	pos.	pos.	pos.	neg.	neg.
B. Muin.	pos.		pos.		neg.	neg.
D. Mat.	pos.	pos.	pos.	pos.	neg.	neg.
L. Mart.	pos.	pos.	pos.	pos.	neg.	neg.
J. F. Es.	pos.		neg.		neg.	neg.
E. Rub.	pos.	pos.	neg.	neg.	neg.	neg.
A. F. Vaz.	pos.	pos.	pos.	pos.	neg.	neg.
M. Ahij.	pos.	pos.	neg.		neg.	neg.
J. J. Pr.	pos.	pos.	neg.		neg.	neg.
M. P. R.	pos.	pos.	pos.	pos.	neg.	neg.
F. Ast.	pos.	pos.	neg.		neg.	neg.
G. Barr.	pos.		neg.		neg.	neg.
A. Font.	pos.	pos.	neg.		neg.	
T. Ben.	pos.	pos.	neg.		neg.	
S. Serr.	weak	neg.	neg.		pos.	pos.
F. Mant.	weak	neg.	neg.		pos.	pos.

on the allergic value of fungi. Some time afterwards, S. Van Leuwen,[26] Hansen,[10] and ourselves,[18] were able to demonstrate sensitization by other fungi that eventually could be cultured from flours *(Aspergillus* and *Penicillium).* We showed not only the passive transmission of allergy by fungi, but also, for the first time, provocation with a pure penicillium culture in one of these cases.

If these imperfect fungi, whose spores can easily be cultured, have in certain types of asthma a significant importance which is continually being confirmed, they have a much smaller value in the type of asthma with which we are dealing. Wittich and Stakman[31] proved sensitization to *Ustilago,* and we have shown[14,16] that *Tilletia* is of fundamental importance in the production of this type of asthma. A systematic study, with extract of rusts and smuts of cereals, has abundantly shown us that *Tilletia* is of greater interest, at least in our country, where this fungus is the most frequently encountered grain parasite. Next in importance comes *Ustilago,* and far behind, *Puccinia;* the three cases, in which we have seen clear sensitization, were farmers and not millworkers, a fact which was not surprising when taking into account the conditions of this infection in the ear of corn. In agreement, however, with the results of observations by Waldbott and Ascher,[29] we have found cases of sensitization to *Tilletia, Ustilago,* and *Puccinia* in individuals who lived in the country but did not have these occupations. This result may be explained if it can be demonstrated that these spores are in the air. We noted in a paper published some years ago,[18] the existence in the air of *chlamydospores,* the nature of which we were not able to establish.

Today we believe that asthma in millworkers and villagers, and generally in those who live in parts where grains are to be found, is almost always due to sensitization by *Tilletia,*[14,15,16,17] the correctness of which

we have proved not only by means of cutaneous reactions but also by passive transfer and with the provocation tests by nasal contact. Never-

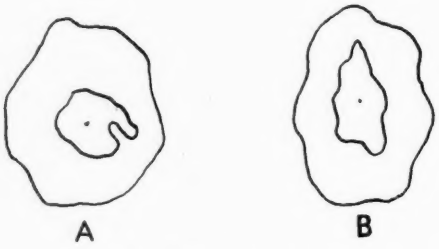

Fig. 1. A and B. Cutaneous reactions.

theless, not all of the cases find a true explanation in the real but infrequent sensitization by flour, in the doubtful sensitization by mites or in the more frequent and proved sensitization by rust and smut. In some cases in which we obtained a positive intradermal reaction and passive transfer to cereal dust, none of these factors gave rise to reaction. Table I, dealing with twenty-four cases of asthma sensitive to cereal dust with positive intradermal reaction (two of them weak), has been reproduced from one of our earlier papers.[12]

Out of this group of twenty-four cases sensitive to cereal dust, proved in many of them by passive transfer, only two were sensitive to flour and of the remaining twenty-two, fourteen were sensitive to *Tilletia,* leaving eight cases which cannot be explained. The possibility remains that we are dealing with independent sensitization that eventually develops owing to variable elements, different in each case, existing in the dust at home. But we made an experiment with the patients, whose result seemed to us very interesting. The first was a man living in the province of Avila and the second a woman living at Ciudad Real, over 200 kilometers away, without any relationship or acquaintance. Both patients had positive passive transfer and reactions to cereal dust but not to clean flour, mites, smuts, and rusts. Notwithstanding, an extract of dust from the granary of one of them (T. Ben.) gave rise to a nasal reaction outbreak in the other (A. Font.). Also, there was a positive reaction in the healthy individual's skin when treated with an injection of serum from the latter patient; the reverse was also positive. We cannot but conclude that the dust taken from these granaries, so far apart from each other, contained an unknown allergen common to both dusts. We had two cases afterwards in which we were able to prove the existence of another source of sensitization: a beetle which frequently parasitizes granaries and corn warehouses.

4. *Calandra granaria.*—A report on the first patient whose case history has allowed us to discuss the possibility, is of interest.

Fig. 2. *Calandra granaria* found in granary dust.

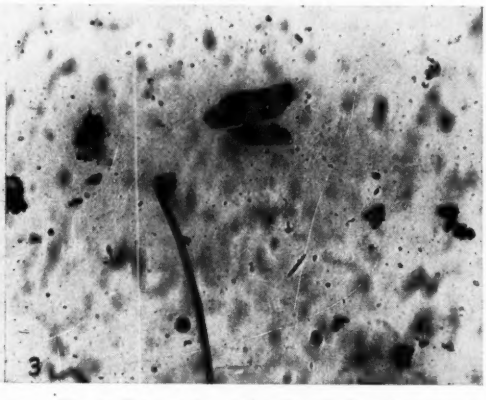

Fig. 3. Granary dust infested with *Calandra granaria.*

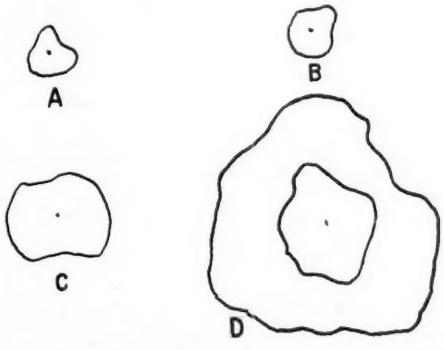

Fig. 4. Passive transfer by Prausnitz-Kustner method. *A.* Normal serum with control. *B.* Patient's serum with control. *C.* Normal serum with extract of *Calandra granaria.* *D.* Patient's serum with extract of *Calandra granaria.*

P. S. Poz., laborer, forty-six years of age, from the province of Jaen, without having had any previous symptoms, noticed, while packing grain for sowing, itching of the nose and sneezing, a dry cough and acute dyspnea crises that forced him to go out into the open air, where all returned to normal in a quarter of an hour. After some time there also appeared some papular and prurigenous spots (urticaria) on the face, neck, and hands. From this time he began to show similar manifestations whenever he was close to the stored grain. On the other hand, he noticed no reaction with clean grain on the threshing floor. His asthma became so bad that he was in bed two months with "status asthmaticus," and finally came to see us. When he left home he got better, and in Madrid all symptoms disappeared. It is

noteworthy that at home he had grain stored, although it was in another room. Physical examination revealed nothing; the white cell count showed marked eosinophilia (6 per cent). The cutaneous and intradermal reactions with all the series of allergens were negative. The reactions obtained with dust from his granary can be seen in Figure 1. As the reactions to flours, fungi, and so forth were negative, we investigated the dust and found that it was strongly infested (Figs. 2 and 3) with a beetle (weevil) which on being studied turned out to be the *Calandra (Sitophilus) granaria* (order *coleoptera*; suborder *Polyphaga;* section *Rhyncophora;* family *Curculionidae)* (see Claus, Grobben, and Kuhn[4]). Extracts of this insect were then prepared, and the intradermal reaction was so acute that we feared for the patient's life. In Figure 1*(B),* the cutaneous reaction can be seen. The same extract gave no reaction whatsoever when cutaneously or intradermally injected in normal individuals. We then tried passive transfer, the result of which can be seen in Figure 4.

In order to make a complete examination, we carried out the precipitin reaction with our technique which has been published elsewhere,[1] and the following results were obtained:

Precipitins for	*Results*
Calandra granaria	positive up to 1:640 dilution.
wheat	negative
barley	negative
cereal dust	negative
vegetable dust	negative

Afterwards, we had another case in which this sensitization was accidentally discovered as we had included it among the allergens we commonly test on asthma patients who come from the countryside.

The patient, Sr. A. Ariz., had never had any signs of asthma and had lived in different European and American countries. Three years earlier he retired from business and went to live in a village near Madrid. Every year since then, mainly in autumn and winter, he suffered asthma crises which did not appear when he was out of the village. They were very acute and generally came at night, and he had not noticed any specific causative influence. No positive results were obtained with the reactions to different allergens (foodstuffs, bacteria, fungi, dust from the home, and so on), but when the test was made with *Calandra granaria* extract, an acute asthma attack was produced which necessitated repeated epinephrin injections. Passive transfer was positive and strong.

DISCUSSION

We have shown that there exist in cereal dust different elements that, acting as causative allergens, can produce sensitization. In order of importance we can mention among them the fungi, insects, acarina, substances in dust, and flour itself.

The fungi of greatest importance are rust, smut and, especially in our own experience, *Tilletia.* They can be found in great quantities in granary dust and in that of milling establishments, owing to their fineness and the ease with which they spread once the covering of the infected grain has broken. The latter, equally with *Ustilago* and *Puccinia,* can spread in the air at the time of seed-falling, thus acting as causative agents in the population at large (Waldbott and Ascher,[29] and Jimenez-Diaz and coworkers[16]). Other fungi, such as *Aspergillus* and *Penicillium,* can have an

influence above all by infecting damp flour, but this is a much rarer occurrence.

Little account has been taken of insects. Besides occupational asthma, with which we are now dealing, in isolated cases this possibility has been revealed, as in sensitization by *trichoptera* (Caddis fly) (Parlato[21]), *ephemerida* (Figley[6]), *Musca domestica* (Jamieson[11]), *Cimex lectularius* (Sternberg,[24] Jimenez-Diaz and S. Cuenca,[19] and Lahoz and Recatero[20]). Wittich[30] has shown sensitization in cases of vegetable asthma by the *Zabrotes* (bean weevil), and Sheldon and Johnston[23] have shown the possibility of sensitization by *coleoptera*. In the case of asthma produced by granary dust, in farmers or people who live in villages where there are near-by granaries, and also in millworkers, our studies show that the sensitizing agent can be a *coleopteron*, the *sitophilus (Calandra granaria)*. We believe that in the future more importance should be given to this possibility.

Sensitization to flour is a quality proved and confirmed over and over again, but it is of most importance among bakers; lastly, we can admit the existence of other still unkown substances in dust, such as the generic substance X in house dust.

SUMMARY

The authors enumerate the factors existing in grain dust which can act as allergens and be the cause of occupational asthma in millworkers, farmers, and so forth. Besides rust and smut, *coleoptera* must be taken into account *(C. granaria)*, and less commonly acarina, flour, and unknown substances similar to those which produce the sensitization action of domestic dust.

REFERENCES

1. Ales, Arjona, Jimenez-Diaz, and Segovia: Rev. Clin. Esp., 19:238, 1945, and 23:13, 1946.
2. Baagoe: By Hansen-Berger's Allergie. Leipzig: Thieme, 1940.
3. Cadham: J.A.M.A., 83:27, 1924.
4. Claus, Grobben and Kuhn: Lehrbuch der Zoologie, 10 Auf. Berlin: Springer, 1932.
5. Coca: Familial Non-Reaginic Food Allergy. 11 ed. Springfield: Thieme, 1945.
6. Figley: Am. J. Med. Sci., 178:338, 1929, and J. Allergy, 11:376, 1940.
7. Frugoni and Ancona: L'asma bronchiale. Torino: Un. Tipogr. Edit., 1927.
8. Grimm: Das Asthma. Jena: Fischer, 1925.
9. Hansen, Rost, and Dekker: Practikum der allergische Krankheiten. Montana-Verlang, 1930.
10. Hansen: Verhandl. d. deutsch. Gesellsch. f. inn. Med., 204-106, 1940.
11. Jamieson: J. Allergy, 1:83, 1938.
12. Jimenez-Diaz, Ales, and Arjona: Rev. Clin. Esp., 15:411, 1944.
13. Jimenez-Diaz: Algunos problemas de la patologia interna. P. 115. Madrid: Cientifico-Medica, 1940.
14. Jimenez-Diaz, Castro, Lahoz, Recatero, and Canto: Rev. Clin. Esp., 1:1, 1940.
15. Jimenez-Diaz: El asma y otras enfermedades alergicas. Madrid, 1932.
16. Jimenez-Diaz, Lahoz, Recatero, and Canto: Rev. Clin. Esp., 2:35, 1941.
17. Jimenez-Diaz: Rev. Clin. Esp., 11:149, 1943.
18. Jimenez-Diaz, S. Cuenca, and Puig: J. Allergy, 3:396, 1932.

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ALLERGY IN GLAUCOMA

Manifestations of Allergy in Three Glaucoma Patients as Determined by the Pulse-Diet Method of Coca

CONRAD BERENS, M.D., LOUIS J. GIRARD, M.D., and EDITH CUMMINGS
New York, New York

DURING the past six years we have been conducting an investigation concerning the etiology of glaucoma, especially that of chronic simple glaucoma, in which ocular hypertension is not preceded by other demonstrable ocular pathology. The role of allergy as a possible predisposing factor in this disease, although receiving scant mention in the literature, seemed worthy of consideration.. Previous reports[1,2] have dealt with the probable role of bacterial allergy, especially of the upper respiratory tract, in the etiology of chronic simple glaucoma. However, the known methods of establishing allergies, particularly the food allergies, appeared too unreliable to warrant the inclusion of such a study. In 1945 our attention was brought to Coca's method[3] of determining allergy by the pulse rate. We also learned that an investigation of the rôle of allergy in the etiology of glaucoma by Coca and the late Mark Schoenberg had been interrupted by the death of the latter. Although the findings were incomplete, the preliminary results were sufficiently suggestive to justify a more extensive study, especially in view of the fact that glaucoma accounts for at least 12 per cent of blindness in the United States of America.

Difficulty was encountered in the selection of suitable cases. Because of the variability of the signs and symptoms of glaucoma, it was desirable that the patient should have been under our observation for a year or more prior to the allergy study and that he had remained so for at least a year after removal of the allergens. In order to evaluate the effect of the removal of any existing allergens from the diet, or the effect of environment upon the ocular condition, it was considered preferable that the affected eye should not have been operated upon prior to the study, or the tension should have been uncontrolled in spite of surgery. However, a progressive loss of visual fields in spite of apparently controlled tension offered a suitable basis for research. Two of the patients had been operated upon and the tension controlled but they continued to show a progressive loss of visual fields. The latter seemed to show improvement after the institution of an allergen-free diet. In the third patient, no operation had been performed and the tension was not controlled until food allergens were eliminated from the diet. It was essential that the patient have no coronary disease which might interfere with the interpretation of the pulse rate, that existing inhalant or contact allergens be suitably controlled, and, above all,

From the Department of Ophthalmology New York University College of Medicine. From a grant made by the Ophthalmological Foundation, Inc.
Read in the Symposium on Allergy of the Academy of Science, April 26, 1947.

that he be intelligent and painstakingly co-operative. Of fifteen patients with glaucoma, all of whom proved to be allergic by preliminary tests, only three met the specified requirements. All three patients discussed in this paper, received autogenous bacterial antigens developed from their own upper respiratory organisms and were treated by a rhinologist, but their glaucoma was seemingly controlled only after their food allergies, as indicated by the pulse-diet method, received attention.

Case Report

Case 1.—Miss J. L. was observed on May 28, 1945, at the age of forty-four. She had had some watering and burning of her eyes six weeks previously and had been to the Brooklyn Eye and Ear Hospital for treatment. It was there she was first told that a condition of "potential glaucoma" was present. She had no other eye symptoms. Her family history was negative, and past medical history uncovered only the presence of a chronic bronchitis (confirmed by roentgenogram) for several years.

Our examination showed: vision, right eye—20/25 correctable to 20/20 with + 1.00D sph. + 0.25D cyl. axis 90°; vision, left eye— 20/30 correctable to 20/20 with + 1.00D sph. + 0.50D cyl. axis 90°. Accommodation was right eye—600 mm. print at 230 mm., and left eye—500 mm. print at 200 mm. The near point could be brought to normal with a +1.00D sph. added to the above correction.

External and slit lamp examinations revealed no pathologic lesions. Tension taken with a Schiötz tonometer was right: 14 mm. Hg., left: 34 mm. Hg. taken with the 5.5 and 7.5 Gm. weights. Similar readings were found one hour later. Her visual field on the stereo-campimeter was normal. Roentgen examination of the patient's sinuses showed thickening of the mucous membranes of the left antrum and clouding of the sphenoids. There was bone absorption about the roots of her left upper central incisor and right upper lateral incisor.

She was seen by a rhinologist who confirmed the findings in the left antrum, ruling out sphenoid disease by irrigation, and in addition diagnosing the presence of a chronic tonsillitis.

Bacteriological studies revealed that toxic Streptococcus viridans was present in large amounts in the throat as well as in the feces. Brucellosis intradermal test was negative but the tuberculin patch test was strongly positive. Basal metabolic rate was minus 9. Her blood count was normal except for a hemoglobin of 76 per cent and a Schilling index of 10.5. Blood chemistry: urea, urea nitrogen, nonprotein nitrogen and cholesterol were above normal.

A buffered solution of pilocarpine 0.5 per cent was prescribed t.i.d. for her left eye, and weekly injections of an autogenous streptococcus vaccine. The tension in her left eye remained elevated on succeeding visits until August 6, 1945, when it was 19 mm. Hg. in each eye. During the interim period she had received treatment to her sinuses, including penicillin locally, by the rhinologist. A visual field taken at this time revealed marked temporal constriction of the left field with a 1 mm. test object. The 2 mm. isopter was normal.

Reculture of the nose and throat on August 9, 1945, again showed toxic streptococci and in addition coliform organisms were found. A coliform vaccine was prepared and given in weekly injections. At this time it was reported that her left upper incisor had been removed and that the sinus infection was "under control."

Observation on October 22, 1945, revealed a change in the visual field of the affected eye. Central fields showed a baring of the blind spot with the 1 mm. object (Fig. 1) in spite of the fact that tension had remained within normal limits.

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On December 13, 1945, repeat fecal cultures showed almost complete absence of coliform bacteria and 150,000 toxic streptococci per dry gram. Tension was normal. Chest roentgenogram revealed no disease.

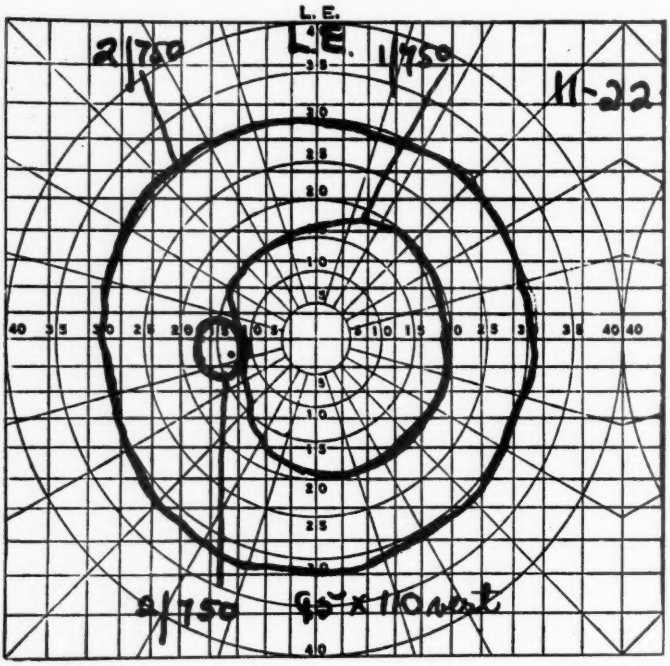

Fig. 1. Left visual field of Mrs. J. L., taken on November 22, 1945, showing temporal contraction of the 1 mm. isopter with baring of the blind spot; 2 mm. isopter is normal.

On January 13, 1946, the patient was started on an allergy study using the pulse-diet method for determining food allergies.

A few days later the patient developed an acute upper respiratory infection which was followed by empyema of the left antrum. This was treated by the rhinologist and on January 25, 1946, he performed an antrotomy. He found a great amount of pus and thickened membranes.

On February 19, 1946, she was placed on a non-allergic diet. The pulse-diet method had shown allergies to potato, cereals, sugar, milk, tomatoes and peanuts.

On March 25, 1946, her visual field again showed baring of the blind spot with the 1 mm. object but a definite improvement over that field taken in October.

She was observed at monthly intervals from March to December with no particular change in the tension. Repeated visual fields remained the same.

On April 15, 1947, after an absence of four months during which time she remained on her allergen-free diet and received her autogenous streptococcus and coliform vaccines, her visual field showed improvement over previous fields. There was no baring of the blind spot in the left eye and the 2 mm. isopter was normal (Fig. 2).

Follow-up and Highlights.—This case is not so dramatic as the other

two cases we shall report because the ocular condition before starting the allergy study was not so serious. Her tension was brought under control by pilocarpine before the allergen-free diet was instituted. Her vision

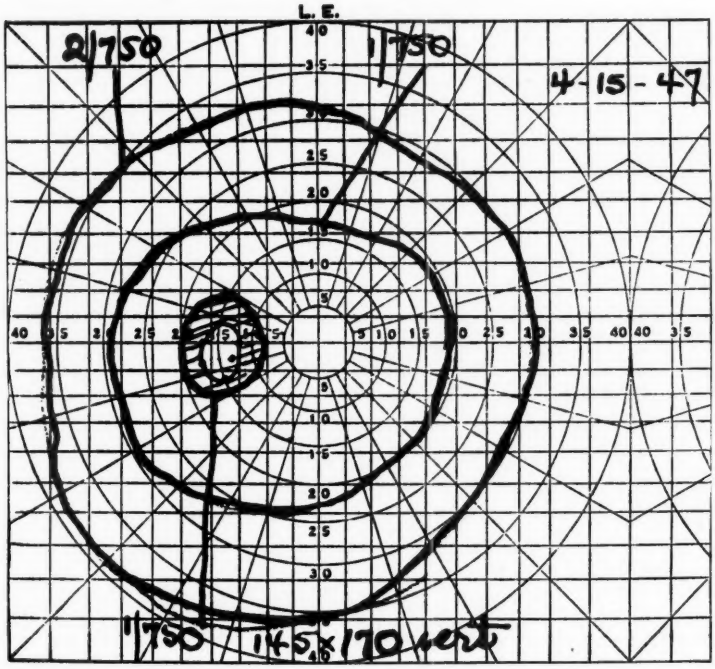

Fig. 2. Left visual field of Mrs. J. L., taken on April 15, 1947, showing improvement of 1 mm. isopter and no baring of the blind spot.

is and was approximately normal with slight fluctuations. Visual acuity is usually the last ocular function to be affected in glaucoma.

Two visual fields taken after going on the non-allergic diet were normal, whereas before the institution of the diet there was progressive constriction of the smaller isopters with baring of the blind spot. This was the most marked ocular improvement.

Associated symptoms of chronic constipation completely disappeared after the institution of the diet.

Case 2.—Mrs. I. E., aged forty-six, was first observed on December 12, 1943. She had been treated four years previously for glaucoma of her right eye. She was complaining of sharp pain over her right eye.

Examination: Vision corrected, right eye—HM at 1 foot; left eye—20/15. The right eyelids were edematous and red, the bulbar conjunctiva was deeply congested.

The anterior chamber was shallow, the pupil was dilated and fixed. There was typical glaucomatous cupping of the optic disc (8 diopters) and pallor of the nerve. Tension with Schiötz tonometer right eye 30 mm. Hg., left eye 12 mm. Hg.

Her visual field was reported as: right eye, light field at 2 inches, only small temporal field of perception nasally, above and below. Left eye, slight contraction above and below nasally with 1 mm. object. Absolute scotoma above the blind spot with 1 mm. object. Blind spot enlarged.

Roentgen examination of her sinuses revealed slight clouding of the ethmoids, and marked clouding of the left antrum with thickening of the mucosa. There seemed to be fluid in the right antrum. The sphenoids were cloudy, the right more than the left.

The rhinologist verified the fact that there was infection in the sinuses and advised sulfadiazine treatments by the Proetz method.

Hemotology studies were reported as normal except for a high Schilling Index (38).

Cultures taken from the nose, throat and feces showed B. coli and Strep. viridans in the throat, and highly toxic (to *in vitro* tests) Streptococcus viridans in the feces.

A 2 per cent solution of pilocarpine was prescribed for the right eye q.i.d. and weekly injections of an autogenous coliform vaccine advised. She was treated simultaneously for her sinus infection.

In spite of this treatment, she returned two weeks later in acute distress with her right eye. Examination showed her tension had risen to 56 mm. Hg. in that eye. She was treated in the office with pilocarpine 2 per cent and eserine packs. This failed to lower the tension perceptably and she was given a retrobulbar injection of 1.5 c.c. of 2 per cent novocaine. Her tension dropped to 40 mm. Hg.

Within another two weeks her tension had again risen to 60 mm. Hg. in her right eye and she was admitted to the hospital.

On January 21, 1944, under local anesthesia, an iridocorneosclerectomy was performed on the right eye. Postoperative recovery was uneventful. Her tension remained subnormal for one month and then began to gradually rise. Her visual field in the right eye taken on March 24, 1944, showed a small area of vision in the lower temporal field taken with the 20 mm. object. Her light field was slightly larger. The left visual field was unchanged.

During the next week her tension gradually rose in spite of increasing strengths of pilocarpine and eserine. On April 3, 1944, it was recorded as right eye—56 mm. Hg., left eye—19 mm. Hg. On April 4, 1944, iridocorneosclerectomy and iridencleisis were performed. Following this procedure the tension in her right eye stayed down only two weeks and again rose to 47 mm. Hg., necessitating a retrobulbar injection of alcohol. Her tension fell to normal (23.5 mm. Hg.) but during the next month demonstrated a progressive rise and remained high but the eye was not painful. The tension remained high for several months and then fell to normal.

In October, 1945, her tension again began to rise, this time not only in the almost-blind eye, but in the good left eye as well. (Right eye—34 mm. Hg, left eye—32 mm. Hg). Her visual field at this point was reported as: right eye—small seeing area with 20 mm. object and light temporally; left eye—temporal contraction of the 1 mm. isopter with baring of the blind spot.

In an effort to determine the cause of the continuing hypertension and contraction of the visual fields and thereby retain the vision in the left eye, allergy studies were made by the pulse-diet method of Coca. Major food allergies were found to be: chicken, peas, beans, peanuts, lettuce, wine, eggs, cauliflower, cabbage, brussel sprouts and brocolli.

Two weeks after being placed on an allergen-free diet, this patient's tension, using the same strength of pilocarpine, taking the tension at the same time of day and

after the same post-miotic interval, was recorded as within normal limits (right eye—25 mm. Hg., left eye—25 mm. of Hg.). Five weeks later the tension was right eye—17 mm. Hg., left eye—20 mm. Hg.

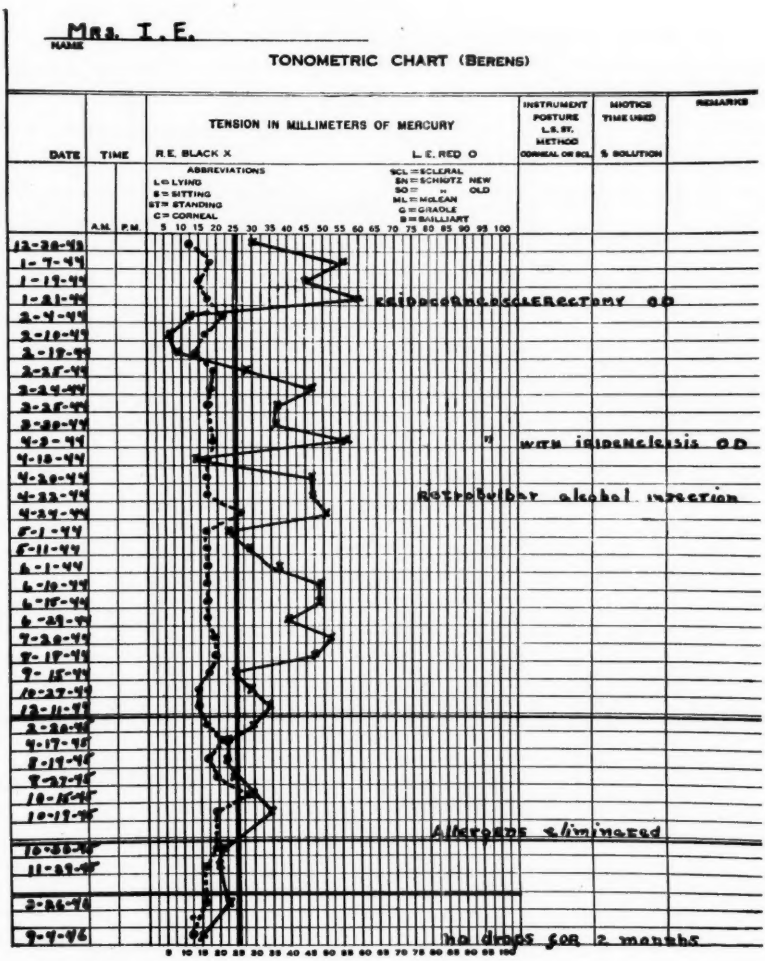

Fig. 3. Tonometric chart of Mrs. I. E. Note that tension remained normal for one year after the elimination of allergens.

She was not observed again until September 4, 1946, when after using no pilocarpine for two months previously, her tension was right eye—16 mm. Hg.; left eye—13 mm. Hg. Vision was right eye—HM; left eye—20/15 with correction.

Follow-up and Highlights.—This patient had glaucoma of both eyes with uncontrolled tension in her right eye in spite of repeated operative

intervention and intensive medical therapy. There was beginning hypertension in the left eye. Following the institution of an allergen-free diet, the tension became normal in both eyes even after cessation of all medication (Fig. 3).

Associated allergic symptoms were severe gastrointestinal distress and chronic constipation. Within two weeks after adhering to the allergen-free diet and without the customary cathartics, the patient's elimination was normal for the first time in the patient's memory.

It is a recognized fact among most ophthalmologists that emotional stress or worry has a direct effect on the ocular tension of the glaucomatous patient. In this particular case, at least some of the tension rise during the stormiest period could be attributed to the patient's worry over, and subsequent loss of her brother (about the time of the retrobulbar injection). Another similar experience would be expected to have a similar result, yet, during 1946, while on her allergen-free diet, the patient went through a severe emotional and physical experience involving the near fatal illness of her only son. With special permission from the Navy Department she nursed him eight to ten hours a day for three months. At no time did her eyes bother her, nor was there any rise in tension in spite of not using miotics. Since glaucomatous patients usually are as dependent on miotics as diabetics are on insulin, it was a good test of the possible benefit resulting from the allergen-free diet.

Case 3.—Miss E. H., aged sixty-seven, a retired school teacher, was examined on March 3, 1941. On her first visit her vision was right eye—20/100 correctable to 20/20 with + 2.25D cyl. axis 100°; left eye—20/100 correctable to 20/20 with a + 2.25D cyl. axis 85°. With a + 2.50D added to the above correction, she could read 400 mm. print at 290 mm. with each eye. Her tension was recorded as right eye—40 mm. Hg.; left eye—26 mm. Hg. with the Schiötz tonometer and a 7.5 gm. weight. The anterior chamber of each eye was shallow, otherwise the external examination was normal. Both lenses showed finely granular cortical opacities.

Her visual field was recorded as right eye—slight enlargement of the blind spot, slight concentric contraction with 1 mm. test object, and slight contraction for all colors; left eye—enlarged blind spot and temporal and inferior contraction with 1 mm. test object.

Her general physician reported a right radiculitis and a hypertrophic cervical arthritis.

Laboratory studies revealed a moderate secondary anemia with a sedimentation rate of 18 mm. per hour and a Schilling Index of 62. Cultures from her nasopharynx demonstrated numerous toxic hemolytic streptococci and Streptococcus viridans.

The patient was placed on pilocarpine 2 per cent b.i.d. for her right eye and hot compresses and massage for both eyes. Under this regime her tension came down and remained within normal limits for seven months. During this time she had no pain but complained of attacks of blurring of vision in her right eye. Her visual field remained approximately the same and she was placed on an autogenous streptococcus vaccine.

On November 10, 1941, she complained of acute pain in her right eye following a severe cold. Her vision in the right eye was 3/200; her tension was right eye—44 mm. Hg.; left eye—14 mm. Hg. with the 7.5 gm. weight. Her last pilocarpine

drops had been taken only two hours previous to the examination. Under the slit lamp the cornea showed clouding and the iris was congested.

She was placed in the hospital and an iridocornesoclerectomy performed that same day. Her postoperative recovery was good but her corrected vision in her right

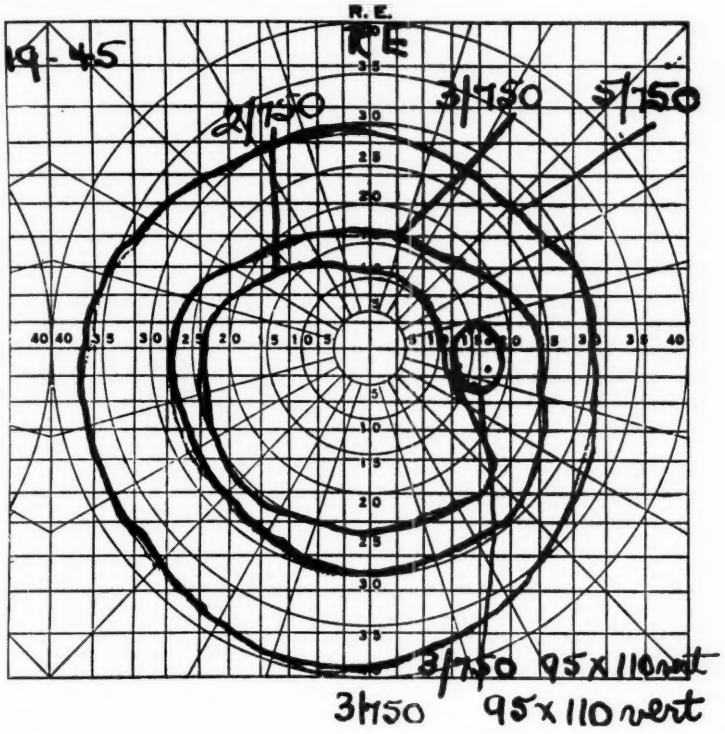

Fig. 4. Right visual field of Miss E. H., taken on October 19, 1945, showing marked temporal contraction of all isopters and baring of the blind spot.

eye was reduced to 20/100. She was observed periodically during the next two years. Her tension remained normal but her vision continued to be poor in the right eye. Repeated visual fields continued to show contraction of her right field. Toward the end of this period her vision began to fail (going down to 20/200 in her right eye) and there was progressive contraction of her visual fields.

At this point (September, 1945), the patient was investigated for possible food allergies. These studies covered a period of approximately two months. The pulse-diet method revealed the following major allergens: wheat, all cheese, oatmeal, coconut, pork (including jello with a pork base), vinegar and citrus fruits and Lavor s. Questionable allergens included beans, milk, lettuce, V-8 vegetable juice, the apricc family and coffee.

The patient claimed subjective general and visual improvement soon after she was placed on the allergen-free diet.

Her last field before starting the allergen-free diet was taken on October 19, 1945. It was similar to those taken previously showing upper temporal loss in all isopters and baring of the blind spot (Fig. 4).

In November, 1945, there was definite improvement in the visual field of the right eye for the 3 mm. isopter and slight improvement in the 2 mm. isopter.

Six months later, June, 1946, the improvement was even more marked, 2 and 3 mm. isopters had filled out and there was no longer a baring of the blind spot.

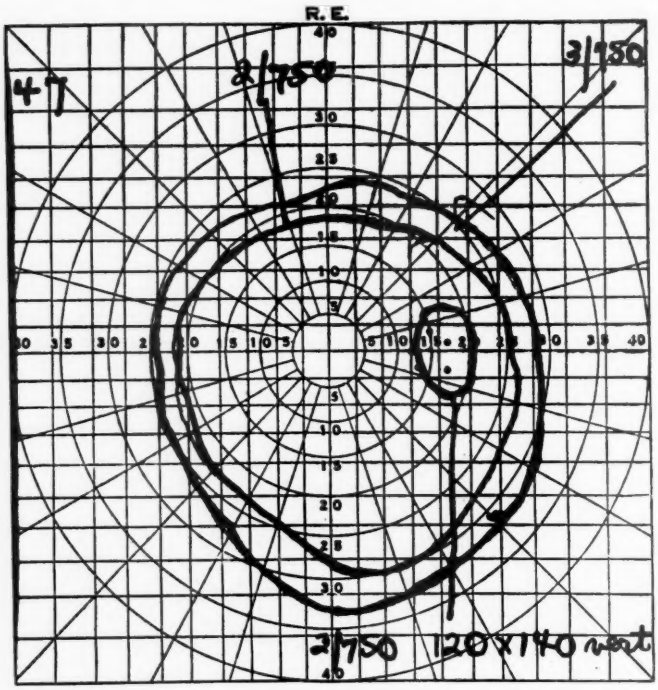

Fig. 5. Right visual field of Miss E. H., taken on February 14, 1947, showing normal 2 mm. and 3 mm. isopters and no baring of the blind spot.

The last field taken on this patient was on February 14, 1947, (Fig. 5) and was the most normal field taken since the onset of the patient's glaucoma.

Follow-up and Highlights.—The patient was placed on her non-allergic diet on December 20, 1945. On January 4, 1946, her vision in the right eye was 20/200, but on January 31, 1947, it had risen to 20/100 and it has remained at this point up to the present in spite of an increase in density of the cataract in that eye.

The field taken on June 6, 1946, six months after initiating the allergen-free diet showed a definite improvement over the previous fields. This was an unusual finding since loss of visual fields associated with optic

nerve damage is usually irreversible. The most that can be hoped for usually is the maintenance of the field without further loss.

Fields were taken on February 14, 1947, and further improvement over June was noted.

It is important to state that the technician who took these fields was the same one who had previously taken them during the two-year period when a progressive loss was observed. Also, the tests were standardized as to lighting (7.5 foot-candles), the size of the test objects, and other factors.

It was also interesting to note that other allergic symptoms, i.e. chronic rhinitis, coughing attacks after meals, eczema, chronic constipation with flatulence and gastrointestinal distress, and neuralgic pains in the neck and face were no longer complained of after the institution of the allergen-free diet.

It may be mentioned that in July, 1945, this patient made application for assistance in learning Braille and for entering a home for the blind. Her psychologic reactions have so improved that she has now abandoned these ideas.

Summary

Three cases of chronic simple glaucoma have been presented in which the usual treatment with miotics and attempted desensitization with autogenous bacterial antigens had been supplemented by the removal from their diets of food allergens, as determined by the pulse-diet method. In one case, the hitherto uncontrolled tension was brought under control apparently only after the institution of an allergen-free diet. In the other two cases, surgery and medical treatment controlled the glaucomatous hypertension but failed to check progressive loss of visual fields. The latter showed marked improvement after the institution of an allergen-free diet.

In view of the many uncontrollable factors involved in the treatment of glaucoma from the psychological, medical and ocular viewpoints it is inadvisable to draw definite conclusions. However, because of the suggestive findings in these cases, it was thought warranted to report them with the hope that the possible role of allergic factors in glaucoma will be investigated by others and the effect of anti-allergic treatment of this most serious disease will receive final evaluation.

Bibliography

1. Berens, C., and Nilson, E. L.: Etiology of so-called chronic simple glaucoma probable role of focal infection, especially of the nasal accessory sinuses. Tr. Am. Acad. Ophth. & Otolaryng., (Jan.-Feb.) 1944.
2. Berens, C., and Nilson, E. L.: Ocular conditions associated with coliform bacteria clinical and experimental observations of coliform bacterial infections of the upper respiratory tract. Arch. Ophth., 26:816, (Nov.) 1941.
3. Coca, A. F.: Familial Nonreaginic Food Allergy. 2nd. Ed. Springfield, Illinois: Charles C. Thomas, 1945.

ANTI-ASTHMATIC EFFECTS OF A NEW SYNTHETIC ANTISPASMODIC

Beta-Diethylaminoethyl 9, 10-Dihydroanthracene-9-Carboxylate Hydrochloride

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SINCE bronchospasm is part of the disordered physiology of asthma, clinicians are interested in new antispasmodics. If the spasmolytic agent is one which counteracts many of the pharmacologic effects of histamine, indicted as the intermediary between antigen-antibody reactions and clinical manifestations, that interest is doubly keen. Such a compound is Beta-Diethylaminoethyl 9,10-Dihydroanthracene-9-Carboxylate Hydrochloride, hereafter more simply referred to as Compound No. 887.

Antispasmodics are of two general types[6]: Those which are musculotropic, such as the nitrites and papaverine, are tested pharmacologically against histamine phosphate (2×10^{-6} gm./c.c.) and barium chloride (10^{-4} gm./c.c.). Those which are neurotropic, such as atropine and scopolamine, are tested against acetylcholine bromide (10^{-6} gm./c.c.). The more peripherally acting musculotropic group would be of most interest to the allergist even without the concept of histamine antagonism. Marked bronchospasm can also contribute to mucosal edema by impairment of lymphatic drainage.[2]

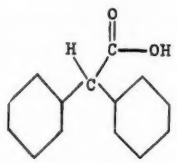
Combinations of various amino-alcohols and chemical modifications of diphenyl-acetic acid have been known to be antispasmodic. The amino-alcohol determines the nature of the action, while its intensity is modified by the acid group employed. Many of these compounds have local anesthetic action, which appears to correlate more closely with musculotropic action than with other properties.[4]

Compound No. 887 is a pure white crystalline substance with a melting point of 170° C. Its basic alcohol, beta-diethylaminoethanol, is a well known compound. The acid, 9,10-dihydroanthracene-9-carboxylic acid, is prepared as follows[1]: A solution of n-butyllithium, prepared in the usual manner from 127.4 gm. (0.93 mole) of n-butyl bromide and 10 gm. (1.44 atoms) of lithium in 1,000 c.c. of absolute ether, is siphoned under a stream of nitrogen into a stirred suspension of 82 gm. (0.45 mole) of 9,10-dihydroanthracene in 400 c.c. of ether. The rate of addition of the butyllithium solution is regulated to produce moderate refluxing. The mixture is then stirred for one hour at laboratory temperature and finally refluxed for three hours. Carbonation with crushed dry-ice, followed by extraction with water and acidification, yields 77 grams of the desired acid, melting at 203° to 204° C. Combination of the acid with the chloride of the amino-alcohol to form the desired ester is carried out in isopropanol solution (Fig. 1).

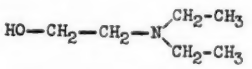
The resulting ester No. 887 is, in general, twenty times more potent than papaverine and one-fifth as effective as epinephrine in relaxing

The product used in these investigations was supplied through the courtesy of G. D. Searle & Co.

spasm of the bronchioles induced in experimental animals by histamine.[1] Guinea pigs are protected against death from intravenously administered histamine, and spasm of the guinea pig ileum is relaxed.[5] Perfusion of the guinea pig lung produces bronchodilation. Bronchoconstriction in bar-



Diphenyl-Acetic Acid



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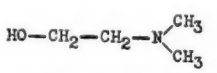

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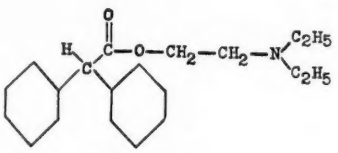

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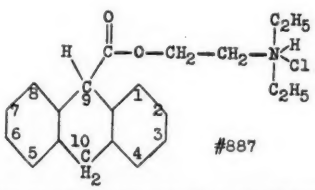

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Beta-diethylaminoethyl 9,10-Dihydro-anthracene-9-Carboxylate Hydrochloride

Fig. 1. Structural relationships of Compound No. 887.

bitalized dogs from both acetylcholine and histamine is antagonized. The vasodepressor effect of intravenous histamine is reduced at least 50 per cent by pretreatment with Compound No. 887. The vasopressor effect of epinephrine in cats is reduced and may be reversed. Local anesthetic action is well demonstrated on the rabbit's cornea. A central hypnotic action, minor in animals, is significantly present in humans.

The following data on toxicity were derived from animal experimentation.[3] The LD_{50} dose, (fatal to one-half of the animals used) was determined by various methods, listed below:

Rats—Intraperitoneal Injection	LD_{50} 0.18	gm./kg.	
Rats—Stomach tube	LD_{50} 1.10	gm./kg.	
Mice—Subcutaneously	LD_{50} 0.60	gm./kg.	
Mice—Intraperitoneal injection	LD_{50} 0.17	gm./kg.	(0.16)*
Mice—Stomach tube	LD_{50} 0.45	gm./kg.	(0.425)*
Mice—Intravenously	LD_{50} 0.027	gm./kg.	(0.017)*

Using the lowest LD_{50} dose found in animals by the stomach tube method (0.45 gm./kg.) as a basis for calculation of the human LD_{50} dose, one would arrive at a figure of 31.5 gm. for a 70 kg. adult. Inasmuch as the dosage used clinically should rarely exceed 0.2 gm. orally, there is a very evident large margin of safety.

*Figures in parentheses are from an earlier and smaller series.

CRITERIA EMPLOYED IN CLINICAL TRIALS

The following objective criteria for the relief of asthma were employed: disappearance or marked diminution of rhonchi; relief of dyspnea with shortening of the phase of expiration; increase in vital capacity.

The subjective criteria used were: diminution or disappearance of wheezing, shortness of breath and coughing; ability to sleep horizontally after previous orthopnea; enjoyment of nights of rest after previously consistently disturbed nights.

During these investigations a definite effort was made to exclude that 25 per cent of asthmatic patients who admit or claim temporary benefit of some degree from any medication, however inert.

OBJECTIVE DETERMINATION OF MINIMUM AND OPTIMUM EFFECTIVE DOSAGE

In the first group of thirty adult ambulatory asthmatic patients an effort was made to determine the minimum and optimum effective dosage. The types of asthma represented were the extrinsic, the intrinsic, and the combined; the sexes were equally represented.

A dosage of 0.1 gm. every four hours was prescribed, with the following results:

Complete relief	8	(Group 1)
Partial relief	4	(Group 2)
No relief	18	(Group 3)
Total	30	Cases

In the completely relieved group of eight, seven had some sedative effect, variously described as calmness or "dopiness." Three of the non-relieved were similarly affected. No vertigo or nausea was reported.

The dosage was then raised to 0.2 gm. every four hours in each of the above subgroups. The first group continued to manifest complete relief, but the sedative effect was heightened in every case, so that only five of the eight were able to perform their usual tasks without falling asleep. The other three fell asleep during the day. One instance of vertigo was encountered.

The four patients in Group 2, partially relieved before, were now completely relieved, but experienced varying degrees of sedation or hypnosis. One instance of nausea occurred.

An additional thirteen of the previously unrelieved eighteen in Group 3 now experienced more or less relief of asthma, but the number noting hypnotic effects increased from three to seven. One instance each of nausea and dizziness was encountered.

The five persons who received no relief from the 0.2 gm. dose were given 0.3 gm. and then 0.4 gm. doses without relief but with marked vertigo or sleepiness.

It was evident that the administration of more than 0.2 gm. every four hours was not necessary. At this dosage level, twenty-five of these thirty

patients were relieved of their coughing and wheezing, but sixteen of the twenty-five relieved, experienced various degrees of sedation or hypnosis. At the 0.1 gm. dosage level twelve of these same thirty patients were relieved, seven of the twelve noting some sedative effect. It also became evident that the hypnotic effect, desirable as it might be during hours of sleep, limited the usefulness of the drug during the day.

SUBJECTIVE DETERMINATION OF OPTIMUM DOSAGE

The next group of thirty asthmatic patients, consistent with the first, were told about the dual nature of the drug and were asked to determine their individual optimum dosages, with consideration both to relief of asthma and sedation. These are the assembled reports:

0.2 gm. every four hours	6
0.2 gm. on retiring but only 0.1 gm. every four hours during the day	5
0.1 gm. every four hours	7
0.2 gm. at bedtime only	4
0.05 gm. every four hours	2
No relief at any dosage up to 0.3 gm. every four hours	6
Total	30 cases

The approximate 80 per cent more or less relieved paralleled the first series. The patients when left to their own discretion had a tendency to use the 0.2 gm. doses on retiring and the 0.1 gm. doses during the day.

The conclusions to be reached from the study of the sixty moderately severe but ambulatory cases of asthma in these two groups were: (1) that approximately 80 per cent received appreciable to complete symptomatic relief from Compound No. 887 taken orally, (2) that the effective dosage varied from 0.1 gm. to 0.2 gm. every four hours, and (3) that the hypnotic effect limited the use of the larger doses in the individual case.

EFFECT IN STATUS ASTHMATICUS

The drug was employed as the sole medication in six cases of status asthmaticus, with complete relief in two cases and partial relief in two others. Since these patients were bedridden and under close observation, a dosage of 0.2 gm. every two hours was used initially in every case. In the two cases completely relieved, this dosage had to be reduced after a day to 0.2 gm. every four hours. The two patients partially relieved had their dosage similarly reduced after thirty-six hours because other remedies were added, and after the third day the administration of Compound No. 887 was discontinued. The two patients unrelieved after one day were changed to other medication.

EFFECT ON ASTHMATIC CHILDREN

Nine children between the ages of five and nine were treated with doses proportionate to their body weight based on 0.2 gm. for a 70 kg. adult. The percentage of symptomatic relief paralleled the adult series, seven

of the nine being benefited. The hypnotic effect seemed more marked, and two instances of nausea and four of "dizziness" occurred. Two of these "dizzy" children presented muscular in-coördination and slurred, incoherent speech.

COMPARISON WITH A STANDARD SEDATIVE-ANTISPASMODIC COMBINATION

A group of fifteen adults having regular nocturnal attacks only were subjected to the following experiment. Every night of the first and third weeks they took 0.1 gm. sodium pentobarbital and 0.2 gm. aminophylline at bedtime. Every night of the second and fourth weeks they took 0.2 gm. of Compound No. 887 at bedtime. The object was to ascertain how effective Compound No. 887 was as a combined antispasmodic and sedative compared to a standard combination of known efficacy.

Compound No. 887 preferred	7
Sodium pentobarbital-aminophylline preferred	4
No preference	4
Total	15 cases

EFFECTS OF PROLONGED ADMINISTRATION

Five patients who used the drug constantly and four patients who used it intermittently in doses of 0.1 or 0.2 gm. four times daily were followed for three months with fortnightly urinalyses, complete blood counts, and fasting blood nonprotein nitrogen determinations. Nothing other than the slight normal variations usually found was noted. Of interest to allergists was that no change in the total number or percentage of eosinophiles occurred in any case.

Six patients taking 0.2 gm. each night were followed for five weeks with the same check-up at weekly intervals, and no significant variations were encountered. In none of these eleven cases was there an instance of either habituation or loss of tolerance to the drug.

SUMMARY AND CONCLUSIONS

The author's conclusions, based on ninety cases treated orally with Beta-Diethylaminoethyl 9,10-Dihydroanthracene-9-Carboxylate Hydrochloride (Compound No. 887) is that it is a safe and useful anti-asthmatic remedy, combining antispasmodic and sedative action. The latter effect somewhat limits its usefulness for daytime use, but it is a valuable feature at night because of the tendency of asthma attacks to occur more frequently or only at night. A dose of 0.2 gm. every four hours rarely need be exceeded, and half that may suffice. A bedtime dose of 0.2 gm. furnishes acceptable symptomatic relief to the majority of people suffering from nocturnal attacks only. The only important side-effect is

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METHODS FOR THE OBJECTIVE DEMONSTRATION OF SUSPECTED DRUG SENSITIVITY

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IN medical practice there often arises the problem of deciding whether a patient's fever, skin eruption, or leukopenia represents an allergic reaction to a certain medication or is an integral part of the disease from which he is suffering. The treatment, diagnosis and ultimate prognosis may rest upon the answer.

This question has faced us repeatedly. All too often we have not been able to answer it satisfactorily. For this reason, we believe that a review of the fundamental nature of the problem is in order, and also an analysis of the techniques which may lead to its solution.

It is essential to limit this discussion to the true manifestations of hypersensitivity. We are not concerned with those reactions which are due to an exaggerated pharmacologic action of a drug. These are toxic reactions and do not represent true allergic states. We are concerned only with those responses which follow prolonged or repeated administration of a therapeutic agent and result in known allergic symptoms, i.e., urticaria, atopic eczema, asthma, et cetera. Bronfenbrenner[3] in 1943 summarized the reasons why such drug reactions should be classified as true allergies.

The only real reason for separating this group of reactions from the other forms of hypersensitivity is *the nature of the antigen.* The antigen is usually not a protein. The antigenicity of these compounds was proven by the fundamental work of Landsteiner on haptenes.[9] Countless simple chemical substances have been shown to be capable of forming antigenic combinations with proteins. It is highly probable that the sensitizing antigen in drug allergy is a drug-protein combination which results from a conjugation with one of the plasma protein fractions.

Allergic disorders produced by the oral administration of drugs are very similar to those produced by sensitivity to foods. Like foods, the oral drug is subject to alteration by the acidity of the stomach, the digestive enzymes, the bacterial flora of the intestinal tract, and the processes of absorption. The simpler drugs are absorbed unchanged. The more complex drugs undergo extensive changes, and the substance finally absorbed may bear little or no resemblance to the original compound. The antigenic properties of this product may vary in antigenic specificity from that of the original drug.

Once absorbed, the compound may be split into simpler units or may be conjugated with other substances. The sulfonamides are acetylated, sodium benzoate is detoxified by glycine. The absorbed drug compound

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can combine with the plasma proteins. Iodine fractions, for instance, may be free or protein-bound. Lastly, there is always the possibility that the drug itself may not actually be a part of the final antigen; this antigen may be some other constituent of the organism which has been specifically altered by the action of the drug. For example, acetanilid may change hemoglobin to methemoglobin or sulfhemoglobin.

There are many reasons, then, why an individual may fail to provide a positive skin test when phenolphthalein is injected into the skin even though the oral administration of this substance produces a violent, bullous erythema multiforme.

To demonstrate drug allergy, the individual problem must be carefully analyzed. The proper method of study can only be determined after the probable pathogenesis of the allergic syndrome is clearly understood. Each drug-sensitive patient must be approached as a new problem, a problem which only in its broadest outlines resembles problems which have been encountered before. There can be little hope of developing a blanket routine which will invariably prove a suspected drug hypersensitivity.

Skin tests.—A positive skin test is dependent upon the reaction of a specific antigen and antibody in the presence of an indicator tissue. In drug sensitivity it may be anticipated that the true antigen will often be difficult to obtain and utilize. However, in the majority of instances, the identity of the offending agent will be suspected. Wholesale testing will rarely be necessary.

As in other forms of haptene sensitivity, the drug alone may provoke a reaction in a skin sensitive to a drug-protein combination. *In vitro* mixtures of drug and serum or plasma proteins may contain a satisfactory antigen. The serum of individuals receiving the drug in therapeutic or greater quantities may contain the antigenic substance. It may also be possible to synthesize the antigen and then use it for direct skin testing.

The peculiarities of the antigen then make it difficult to develop skin tests for drugs. It may be more profitable to approach the problem by means of the antibody. It is reasonable to expect that at some time the plasma of sensitive individuals will contain the specific antibody. Experiments on sensitivity to simple chemical compounds have shown that these antibodies are present in very low concentration. They are strongest in the plasma a few hours after exposure to small amounts of antigen.

The passive transfer method of testing offers several possibilities. The most straightforward method is the injection of the prepared site with the suspected antigen preparations. The technique developed by Walzer for the detection of the absorption of undigested proteins[14] offers interesting possibilities in that it closely approximates the actual conditions encountered in sensitivity following ingestion of drugs. The serum supposed to contain the antibody is injected into the skin and the drug is then

administered by mouth. This drug would then be subject to all of the processes of digestion, absorption and metabolism which might naturally occur. By the time it reached the prepared site it would stand a good chance of closely approaching the true antigen and, perhaps, of producing a positive reaction. The metabolic processes which influence the antigen may take some time (forty-eight to seventy-two hours) and the skin reaction can be expected to be delayed.

What, then, has been the experience with these more or less standard diagnostic approaches to hypersensitivity when applied to drug allergy? Our own studies are still in the preliminary phase. The literature contains many reports of the successful and unsuccessful application of methods of study.

The *patch test* is occasionally successful. It utilizes the pure drug as antigen. The test is likely to be positive in cases with cutaneous manifestations of hypersensitivity and, of course, contact dermatitis. If the skin is highly reactive, the primary irritating properties of the drug may produce a false positive test. A negative test is of no significance except in the contact sensitivities.

The *intradermal test* with the unaltered drug is roughly comparable to the patch test and is one of the least satisfactory methods for the demonstration of drug allergy.

The *tongue test* suggested by Duke[5] for use in cases of aspirin hypersensitivity consists of placing a small quantity of aspirin on the tip of the tongue. When positive, symptoms occur within one minute. Absorption is stopped by rinsing the mouth with vinegar or dilute acetic acid. This test is worth trying with other drugs. It is of no value in such disturbances as erythema multiforme, drug fever, or agranulocytosis where no immediate symptoms can be expected.

Blank[2] succeeded in demonstrating sensitivity to aspirin, sulfadiazine, sulfathiazole, and codeine by holding a tablet of the drug against the *buccal mucous membrane* for ten to twenty minutes.

The immediate reaction is edema and perhaps vesiculation. The twenty-four-hour reaction is vesiculation.

The *conjunctival test* has been used occasionally with success. This method seems to be particularly useful in demonstrating sensitivity to diodrast before it is given intravenously.

The *depression of the blood leukocyte count* following the ingestion of an allergen has been used as a method to test for food hypersensitivity.[7] This procedure may be applicable to drug allergy. So far there are no reports of its use in the literature. In a single instance of lipiodol hyper-

sensitivity, we observed no change in the total or differential leukocyte counts following oral administration of iodine.

The only other test of value utilizing the unaltered drug is the absolute *test of readministration.* If a given syndrome is caused by an allergic reaction to a non-protein medication, it is inconceivable that the identical readministration of the drug should fail to reproduce the syndrome. This method is simple and decisive. When dealing with minor allergic syndromes which do not endanger life or threaten permanent damage to the individual, it is superfluous to waste time and effort with other, more elaborate forms of testing.

Tests utilizing *mixtures of drug and blood serum* have been especially promising. Two types of such preparations have been tried: those obtained *in vitro,* and those provoked *in vivo.* Dameshek and Colmes[4] and Austin[1] prepared an antigen by mixing a solution of aminopyrine with serum, and allowing it to age at 4° C. This antigen gave positive intradermal reactions in patients with agranulocytosis caused by aminopyrine.

Hypersensitivity to the sulfonamide drugs has been demonstrated nicely by Leftwich.[11] He used the serum of patients receiving sulfonamide medication and obtained reactions (wheal and erythema) in twenty-eight of thirty patients who showed clinical evidence of sensitivity to these drugs. The best reactions were obtained with sera having a sulfonamide level of greater than 2 mg./100 c.c. and from patients who had received the drug for more than five days. Fink, Burton and Wheeler[6] failed when they applied this method in children with sulfonamide hypersensitivity.

The *passive transfer test* has proven most disappointing, even in the experimental drug allergies, when the nature of the sensitizing antigen is known.[10]

Walzer's technique of demonstrating indirectly the passive transfer of sensitivity by the oral administration of the antigen has not been extensively employed in the study of drug allergy. Lang and Der[12] report the use of this method in the experimental animal sensitized to quinine, iodine, and neoarsphenamine. Kenedy[8] was able to transfer hypersensitivity, passively, to phenolphthalein in man. He gave the drug twenty-four and four hours before the intradermal injection of serum obtained from a phenolphthalein-sensitive individual. This method is successful when the antibody titer is too low to be detected by the classic passive transfer. It might prove worth while in the study of drug allergy.

When large bullae are present, passive transfer tests might be attempted with fluid aspirated from these lesions. Mixtures of blister fluid and of the suspected drugs may prove valuable for direct skin tests.

Many years ago Oriel[13] succeeded in isolating an aspirin-proteose compound from the urine of a patient with allergic edema due to acetylsalicylic acid. This compound gave positive intradermal reactions, while both the pure drug and the proteose alone failed to do so.

SUMMARY

The following techniques are available for the study of drug hypersensitivity:

1. *Tests using pure, unaltered drug as antigen.*
   - Patch test.
   - Intradermal test.
   - Tongue test.
   - Buccal mucous membrane test.
   - Conjunctival test.
   - Leukopenic test.
   - Readministration.
2. *Tests using combinations of drug and serum proteins.*
   - Drug and serum *in vitro.*
   - Drug and serum *in vivo.*
3. *Passive transfer tests.*
   - Prausnitz—Kuestner.
   - Oral antigen.
   - Intravenous antigen.
4. *Miscellaneous.*
   - Blister fluid.
     - Passive transfer.
     - Fluid and drug as antigen for intradermal test.
   - Use of other body fluids and exudates.

CONCLUSION

This review of the mechanism of the production of drug allergy and of the methods available for its demonstration is intended to lessen the pessimism which surrounds this subject. This pessimism can be attributed largely, perhaps, to the failure of any one method of testing to prove valid in all of the many types of hypersensitivity produced by the myriad of drugs now in daily use. The greatest emphasis should be placed on the pathogenesis of the disorder in the individual patient. More or less standard techniques of study can then be applied at the strategic points which are most likely to be susceptible to testing. Such an approach will not always be successful. However, this should prove more valuable than a rigid adherence to one routine of testing, or a pessimistic abandonment of all forms of skin testing in cases of suspected drug sensitivity.

REFERENCES

1. Austin, V. T.: Chronic anemia and leukopenia in combined acetanilid and aminopyrine poisoning. J.A.M.A., 120:911-913, 1942.
2. Blank, P.: A survey of allergy in a station hospital. Mil. Surg., 92:419-423, 1943.
3. Bronfenbrenner, J.: Is the hypersensitiveness to chemical and physical agents allergic in nature? J. Allergy, 14:105-115, 1943.
4. Dameshek, W., and Colmes, A.: The effect of drugs in the production of agranulocytosis with particular reference to amidopyrine hypersensitivity. J. Clin. Investigation, 15: 85-97, 1936.

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CHEMICAL INVESTIGATIONS OF GIANT RAGWEED POLLEN

Part I

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THERE have been many attempts by various investigators to isolate in pure form, or at least to characterize chemically, the substances in pollens which are responsible for their allergenic activity. The excellent review of "Chemical Studies on the Allergens in Pollens" by Newell[9] summarized the work in the field to the year 1942, and the recent "Critical Review of the Literature of Pollen Allergens" by Wodehouse and Coca[14] has brought this summary further up to date. In view of the above-mentioned papers, only pertinent references will be cited hereafter.

The application to the study of pollen constituents of physicochemical methods, especially the use of the ultracentrifuge and the electrophoresis cell, has produced much valuable data. Abramson, Moore and Gettner[1,2,3] subjected an extract of ragweed pollen to electrophoretic separation in the Tiselius cell. They found a major unpigmented component of giant ragweed pollen to be present over a pH range of 3.5 to 7.5 without apparent dissociation, although the fraction showed two peaks at pH 3.5. A small quantity of the electrophoretically homogeneous component was isolated. It was named trifidin. By means of ultracentrifuge and diffusion measurements this group of investigators calculated the molecular weight of trifidin to be about 5,000. Trifidin diffused through cellophane, gave protein-like reactions and also a positive carbohydrate test. It produced an allergenic response in ragweed-sensitive patients. The quantity of material isolated by means of the Tiselius technique was of necessity small and for that reason more complete data on the chemical constitution of trifidin are lacking.

In an interesting paper by Rockwell,[10] a procedure was outlined for precipitating an active material from ragweed pollen extract by the simple addition of concentrated hydrochloric acid to the solution. The precipitate so formed was centrifuged, washed, dissolved, and reprecipitated several times. It was then dialyzed and dried at low temperatures in vacuo. From an elementary analysis of the material, Rockwell calculated its molecular weight to be about 4,500. A carbohydrate-content analysis and other data were used to substantiate this figure. The author proposed a flavonol-pentose-protein combination as the structure of the substance.

With the above evidence in mind it was decided to investigate further this relatively low molecular weight, protein-like ragweed-pollen component, with the view to isolating by other chemical means a sufficient

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quantity of the material to make it possible to establish more fully its chemical nature. In working out an isolation procedure, efforts were made to minimize adsorption effects, and at the same time to obtain as much information as possible about the chemical nature of the active compound. The following procedure was employed. An aqueous extract of giant ragweed pollen was dialyzed. The dialysate was subjected to a systematic elimination of various protein components by precipitation with easily removable precipitants. The method was based upon the studies of Hiller and Van Slyke[8] who showed, (1) that trichloracetic acid precipitated proteins but left in solution "albuminoses" and "peptones," (2) that picric acid precipitated protein material down to the amino acid stage, and (3) that phosphotungstic acid precipitated proteins, polypeptides, peptides and even some of the amino acid (and some carbohydrate derivatives as well). It was hoped that by such a systematic study we would not only be enabled to characterize chemically the active material, but also to isolate it.

In order to obtain at least a rough comparative estimate of the allergenic potency of the various extracts and fractions which were isolated from the pollen, all extracts were adjusted so that their final volume would be the same, and then a sample of the solution was taken for testing purposes.

After being passed through a Seitz filter, the extracts were injected intradermally into ragweed-sensitive patients and the size of the wheal measured and recorded as 0 to ++++. A standard ragweed extract containing 0.01 mg. nitrogen per ml., called R 0.01, was injected at the same time for comparative purposes. Nonsensitive individuals were included as controls. The average of the wheal size (number of pluses) was the basis for comparison. When possible, ten to twenty patients were tested with each extract.

In order that we might further determine the specificity of the various fractions, passive transfer experiments by the method of Prausnitz and Kuestner were carried out.

EXTRACTION AND DIALYSIS

Four hundred and fifty grams of commercially available giant ragweed pollen were completely defatted with petroleum ether, dried in a current of purified air and then shaken with 3 liters of distilled water, and allowed to settle overnight in the refrigerator. The supernatant liquid was centrifuged and then filtered. Three more aqueous extractions of the pollen were performed in this manner.

The combined extracts were concentrated to about 400 ml. in an efficient vacuum still. A small amount of insoluble material settled out and was removed by filtration. Since the precipitate was found to be insoluble, even in 0.01 N sodium hydroxide, it was discarded.

After diluting the solution to 2 liters, a 500 ml. portion was dialyzed continuously for fourteen days within a piece of previously tested Visking

cellophane sausage-wrapping of 4 inches circumference. The remainder of the solution was similarly treated. Preliminary experiments indicated that fourteen days was the optimum time for the removal of the diffusible active material. The dialyzing apparatus employed was a modification of the vacuum dialyzing device of Hanke and Koessler,[7] and it has been previously described.[11]

TABLE I. RESULTS OF CHEMICAL TESTS PERFORMED ON EXTRACT 6 D

Biuret	—
Xanthoproteic	+
Picric Acid	+
Trichloracetic Acid	+
Phosphotungstic Acid	+++
Ninhydrin	+++
Molisch	++
Benedict	+
Total Nitrogen	0.020 mg. per ml.

TABLE II. EFFECT OF HEAT ON SKIN REACTIVITY OF EXTRACT

	Skin Reactions Obtained with Dialysate Heated for One Hour to			Skin Reactions with R 0.01
	50° C	75° C	100° C	
Case 1	+++	+++	+++	+++
Case 2	++	+	+	+
Case 3	++	++	++	++
Case 4	++++	++++	++++	++++
Case 5	+++	++	+++	+++
Case 6	+	+	+	++
Case 7	+++	++++	++++	++
Case 8	+	+	+	+
Case 9	++	+	+	+
Case 10	+++	++	+++	+++
Case 11	+	0	+	++
Case 12	++	++	++	++
Case 13	+	+	+	+

The four portions of dialyzed extract were combined, evaporated in vacuo to a small volume and redialyzed. Much material precipitated within the cellophane sac and was preserved for other studies.

All dialysates were combined, evaporated in vacuo to 1 liter and redialyzed. These combined redialysates were evaporated in vacuo to 2 liters. A sample of this solution, labeled 6 D, was tested for activity and found to give approximately the same skin test reactivity as the standard R 0.01. Extract 6 D gave chemical tests listed in Table I.

A small sample of 6 D was immersed for one hour in a bath maintained at 100° C. and then cooled in ice water. A second and third sample were treated similarly; the temperatures maintained being 75° C. and 50° C., respectively. These samples were tested, along with R 0.01, on thirteen patients. Heating seemed to have a very small effect on the skin reactivity of this extract, as may be seen from the data in Table II.

Another small portion of 6 D was divided into two parts. One was

buffered at pH 4 and called 6 D 4; the other buffered at pH 8 and called 6 D 8. Both solutions were treated with an equal volume of a 1:1 mixture of butyl alcohol and chloroform and shaken in a shaking machine for three hours. The mixtures were then centrifuged. All organic solvents and any material which precipitated at the interface of the immiscible liquids were removed.

TABLE III. EXTRACT REACTIVITY AFTER REMOVING PROTEINS

Sample	Average Skin Reactivity (11 cases)
6 D	2.2+
6 D 4	1.8+
6 D 8	1.7+
R 0.01	2.3+

This treatment was repeated until there was no evidence of further precipitation on three successive shakings. All normal proteins should be removed by this procedure. After eliminating dissolved traces of the organic liquids the aqueous extracts were then tested for skin reactivity. The results are given in Table III. Although a small quantity of material from the dialysate 6 D was denatured and precipitated at the water-butyl alcohol-chloroform interface, no great loss in skin reactivity of the extract resulted.

TREATMENT WITH TRICHLORACETIC ACID

Into the 2 liters of 6 D a sufficient quantity of concentrated trichloracetic acid solution was introduced so that the final concentration of the acid was 5 per cent. The mixture was allowed to stand overnight in a refrigerator. A small quantity of dark, finely divided material settled out. This was removed by filtration and discarded.

The clear yellowish-brown filtrate was extracted with ethyl ether in a continuous all-glass extractor. By renewing the ether daily, it required ten days to rid the pollen extract completely of the trichloracetic acid. The resulting solution was brought to pH 7 by the addition of 20 per cent sodium hydroxide and then was evaporated in vacuo to 1 liter. The concentrate was again acidified with trichloracetic acid, allowed to stand in the refrigerator for eighteen hours, filtered, extracted, and neutralized as described above. Finally water was added until the volume was 2 liters. The solution was designated 6 DT.

Eight ragweed-sensitive patients showed 6 DT to be as skin reactive as 6 D, which was comparable in activity to the standard R 0.01. Apparently little or no allergenic activity was removed by trichloracetic acid. Inasmuch as the active material was not precipitated by trichloracetic acid, it could not have been a true protein.

TREATMENT WITH PICRIC ACID

To the 2 liters of 6 DT, one and one-half volumes of saturated picric acid solution were added. After standing in the refrigerator overnight, the material was centrifuged, yielding a clear yellow liquid and a small quantity of dirty yellow precipitate. The solid was discarded. The solution was neutralized, then evaporated in vacuo to about 1 liter. The pH of the liquid was adjusted to 2, and the picric acid was completely removed by ethyl ether in an all-glass continuous extractor. A current of purified air served to remove any dissolved ether from the resulting clear brown solution. Enough 20 per cent sodium hydroxide solution was added to bring the pH to 7. No change in color or clarity resulted.

The liquid was evaporated in vacuo to 500 ml. Again, it was treated with one and one-half volumes of saturated picric acid, allowed to stand for eighteen hours in the refrigerator, centrifuged, extracted, and neutralized as described above. This clear brown liquid, labeled 6 DTP, was diluted to 2 liters and a sample removed for testing.

There was no appreciable change in skin reactivity. Results on fifteen patients showed 6 DTP to be as skin reactive as the standard R 0.01. Apparently the picric acid treatment removed little or none of the active substance. It, therefore, could not have been an "albuminose" or "peptone."

TREATMENT WITH PHOSPHOTUNGSTIC ACID

A solution containing 300 gm. of phosphotungstic acid and 180 ml. of concentrated hydrochloric acid was added to the 2 liters of 6 DTP. Under continuous stirring a heavy, non-homogeneous, greyish precipitate was formed. Standing overnight in the refrigerator resulted in a great increase in the amount of precipitate. The solids were filtered off and washed with ice-cold dilute acidified phosphotungstic acid solution. Inasmuch as some of the precipitate continually dissolved during the washing, the process was discontinued after 500 ml. of wash liquid was employed. The combined filtrate and wash liquids were labeled Y and set aside for subsequent study.

The phosphotungstate precipitate was suspended in water and extracted eight times in a large separatory funnel with 300 ml. portions of a 1:1 amyl alcohol and ethyl ether mixture. A small quantity of the precipitate failed to dissolve during this treatment, even upon further acidification; it was therefore removed and discarded. The solution was extracted twice more with 1:1 amyl alcohol-ether mixture, and then four times with ethyl ether. A current of purified air removed the residual ether from the solution. Testing with $BaCl_2$ proved the absence of any phosphotungstic acid in the liquid. During the first few extractions considerable amounts of reddish-yellow coloring matter were removed. The resulting solution, named 6 DTPF, was clear and light-orange in color.

It was brought to pH 7 by the addition of 20 per cent sodium hydroxide. Water was added until its volume was 2 liters.

Clinical tests on twenty-three patients indicated that 6 DTPF was about two-thirds as skin reactive as the standard R 0.01. Inasmuch as this loss in activity might be partly accounted for by the phosphotungstate which dissolved on washing, it seemed expedient to test solution Y which contained this material.

TABLE IV. RESULTS OF CHEMICAL TESTS PERFORMED ON EXTRACT 6 DTPF

Xanthoproteic	Slight
Hopkins-Cole	Negative
Biuret	Slight (reddish)
Ninhydrin	+++
Molisch	+++
Benedict	Negative

The combined filtrates and washings, Y, were evaporated in vacuo to about 300 ml. The solids which precipitated during the concentration were removed by filtration, but were not washed. The filtrate was extracted with 1:1 amyl alcohol-ether mixture until free of phosphotungstate ion. It was then extracted with ethyl ether, dissolved traces of which were subsequently removed by a current of purified air. On neutralizing with 20 per cent sodium hydroxide, the yellow solution was diluted to 1 liter. A sample was taken for clinical testing.

Examination revealed that Y was about one-third as skin reactive as R 0.01. This represented the one-third loss of skin reactivity of 6 DTPF as compared with 6 DTP which gave the same skin reaction as R 0.01. It would therefore appear that the active component is precipitable by phosphotungstic acid.

In an endeavor to purify the material still further, 15 ml. portions of 6 DTPF were shaken with varying quantities of well-washed Norite A. This accomplished the removal of color from the solution. The resulting filtrates varied from the original reddish-yellow to colorless as the quantity of added Norite was increased. However, skin tests with these filtrates showed an almost total lack of allergenic activity. Subsequent testing of the original 6 DTPF, which had been kept in the refrigerator for thirty days while the above operations were being performed, also registered a total loss of allergenic activity. The reason for this is thus far unknown.

The loss of activity of the extracts at this stage of the work was disappointing, especially since it still leaves in doubt the answer to the question of whether Norite A will remove the color alone or the color plus the activity of this fraction.[4,5,12] While we are repeating and continuing these studies, the results obtained so far seemed to warrant their publication at this time. Chemical tests made on 6 DTPF just prior to the inactivation are listed in Table IV.

DISCUSSION

The investigations above described provide additional evidence that there is present in an aqueous extract of giant ragweed pollen an allergenically active substance that dialyzes through cellophane membranes. Only half of the original allergenic activity could be transferred to the dialysate, even after fourteen days of continuous dialysis with a constant flow of water past the cellophane bag. This finding, coupled with the fact that the fraction which did not diffuse through the dialyzing membrane retained about half of the total activity, constitutes additional evidence for the hypothesis of multiple allergens in pollen extracts.

The fact that the active substance in the dialysate is heat-stable, is not denatured at an interface, is not precipitated by trichloracetic acid nor by picric acid, constitutes proof that it is not a protein in any strict sense of the word—nor is it an "albuminose" or "peptone." Yet the extract yielded qualitative tests for protein groupings as well as for carbohydrates. Phosphotungstic acid did precipitate the allergenically active substance in the dialysate of the pollen extract. This reagent will precipitate peptide-linked compounds of a large range in molecular weight. It will also precipitate some of the amino acids, as well as some of the carbohydrate derivatives. It would appear, therefore, that the active material in the extract dialysate under study was a comparatively low-molecular-weight peptide or carbohydrate, a mixture of the two, or perhaps a nitrogen-containing carbohydrate.

The physical and chemical properties of the material confirm this. Only a comparatively low-molecular-weight compound would dialyze through cellophane. The strong ninhydrin test, given by the extract after the last stage of purification, indicated the presence of amino groups, while the pinkish biuret test indicated a small peptide-linked molecule. However, the strongly positive Molisch test was evidence of the presence of a carbohydrate.

In the last stage of purification the extract was of a light orange color. This color could be removed by Norite A, but with the unfortunate loss of activity at this stage, it was not possible to prove whether or not the loss of color was accompanied by loss of activity.

The method of purification in these investigations differed so drastically from that employed in other researches[6,10,13] on the subject that comparisons are difficult to make. It is hoped, that upon repeating and continuing these experiments, sufficient data will be collected to determine whether or not the active principle in our final fraction is trifidin.

SUMMARY

1. An aqueous extract of defatted giant ragweed pollen was exhaustively dialyzed, about one-half of its allergenic activity appearing in the dialysate.

2. The active principle in the dialysate was heat-stable and not denatured at an interface.

3. The dialysate was further purified by treatment with trichloracetic acid. After the removal of that precipitant, saturated picric acid was added, and then the excess eliminated. Neither treatment precipitated the active principle nor was the skin reactivity of the extract appreciably changed.

4. Phosphotungstic acid precipitated the active principle. Upon ridding the insoluble addition compound of the phosphotungstic acid, thereby making it soluble again, the activity was recovered.

5. The most highly purified fraction yielded a positive ninhydrin, biuret and Molisch test.

REFERENCES

1. Abramson, H. A.; Moore, D. H., and Gettner, H. H.: J. Phys. Chem., 46: 192, 1942.
2. Abramson, H. A.; Moore, D. H., and Gettner, H. H.: Proc. Soc. Exper. Biol. & Med., 46:153, 1941.
3. Abramson, H. A.; Moore, D. H.; Gettner, H. H.; Gagarin, J., and Jennings, L.: J. Am. Chem. Soc., 62:1629, 1940.
4. Brown, E. A., and Benotti, N.: Ohio State M. J., 38:1011, 1942.
5. Caulfield, A. H. W.; Brown, M. H., and Waters, E. T.: J. Allergy, 7:1, 1935.
6. Cohen, N. B., and Friedman, H. J.: J. Allergy, 14:368, 1943.
7. Hanke, M. T., and Koessler, K. K.: J. Biol. Chem., 66:495, 1925.
8. Hiller, A., and Van Slyke, D. D.: J. Biol. Chem., 53:253, 1922.
9. Newell, J. M.: J. Allergy, 13:177, 1942.
10. Rockwell, G. E.: Ann. Allergy, 1:43, 1943.
11. Stone, G. C. H.: J. Chem. Ed., 21:440, 1944.
12. Stull, A.; Cooke, R. A., and Tennant, J.: J. Allergy, 4:455, 1933.
13. Stull, A.; Sherman, W. B., and Hampton, S. F.: J. Allergy, 12:117, 1941.
14. Wodehouse, R. P., and Coca, A. F.: Ann. Allergy, 4:58, 1946.

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19. Jimenez-Diaz and S. Cuenca: J. Allergy, 6:397, 1935.
20. Lahoz y Recatero: Rev. Clin. Esp., 5:361, 1942.
21. Parlato: J. Allergy, 135, 1929, and 307, 1930.
22. Salen and Juhlin-Dannfeldt: Act. Med. Scand., 85:505, 1935.
23. Sheldon and Johnston: J. Allergy, 12:493, 1941.
24. Sternberg: J. Allergy, 1:83, 1939.
25. Van Dishoeck and Roux: J. Allergy, 12:481, 1941.
26. Van Leuwen, S.: Allergische Krankheiten. 11 Auf. Berlin: Springer, 1928.
27. Von Ludwig: Die Milbenplage der Wohnungen. Teubner, 1904.
28. Walker: J.A.M.A., 75:787, 1920.
29. Waldbott and Ascher: Ann. Int. Med., 14:215, 1940.
30. Wittich: J. Allergy, 12:42, 1940.
31. Wittich and Stakman: J. Allergy, 8:189, 1937.

THE APPLICATION OF A TISSUE CULTURE TECHNIQUE IN THE CLINICAL EVALUATION OF BACTERAL HYPERSENSITIVITY

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THE role of bacterial hypersensitivity in various diseased states has been the subject of many reports in the literature. The subject has been reviewed by Rich[5] and Scherago.[8] How extensive a role this phenomenon may play in human disease awaits the development of a more reliable clinical method of testing for hypersensitivity than those methods currently available. The only practical method to date of testing patients for bacterial allergy is by the skin test method. The criticisms of the skin test are many. It is not a sensitive test, in that many apparently normal patients exhibit considerable skin reactivity.[4] It does not lend itself to the quantitative determination of hypersensitivity. The anaphylactic reaction cannot be avoided. The number of tests that can be performed is always limited, and the test is not without danger. Therefore, the tissue culture technique was explored as a possibility for developing a more reliable clinical method for determining the presence of bacterial hypersensitivity.

The use of tissue cultures in the study of bacterial hypersensitivity is based upon the fact that the cells of the body with bacterial hypersensitivity are killed *in vitro* by contact with the specific bacterial protein, whereas such cells from the body with anaphylactic, Arthus or pollen-type sensitivity are not killed *in vitro* by contact with the specific protein.[6]

METHODS AND MATERIALS

Bacterial Antigens.—Unless otherwise noted, the antigens employed in these tests were bacterial filtrates prepared from twenty-four-hour broth cultures. Various species of bacteria maintained on blood agar were subinoculated into broth tubes and incubated at 37° C for twenty-four hours. At the end of this time the culture was centrifuged and the clear supernatant fluid put through a Seitz filter. Appropriate sterility tests were performed as a check on the filtrate. Dilutions of the filtrate were prepared in physiological saline solution.

Preparation of the Buffy Coat.—Nine cubic centimeters of freshly drawn blood were immediately added to 1 c.c. of a 2 per cent sodium citrate solution and then centrifuged. The plasma was removed and the buffy coat coagulated by the addition of calcium Ringer's solution. The buffy coat was easily separated from most of the red cells by repeatedly teasing the red cell strands and washing with Ringer's solution. The buffy coat was kept in Ringer's solution until used.

Method of Performing the Test.—The buffy coat was placed on a large black rubber stopper and explants were prepared using a 1.5 mm. corneo-

TABLE I. PATIENTS SHOWING TITERS OF 1:1000 OR HIGHER AGAINST VARIOUS ANTIGENS

Patient	Antigen	Titer†	Clinical Diagnosis
GD	H-Streptococcus	1:10,000	Rheumatoid arthritis—1 year
	Gr-Streptococcus	1:5,000	Bilateral uveitis—6 months
GB	Staphlococcus aureus	1:10,000	Asthma—5 years
TO	H-Streptococcus	1:5,000	Rheumatoid arthritis—20 years
	H-Staphlococcus	1:10,000	
	Gr-Streptococcus	1:5,000	
SK	H-Streptococcus, pneumococcus mixed vaccine*	1:5,000	Recurrent keratitis, bilateral—10 years
	Pneumococcus Type I	1:1,000	

† Highest dilution of antigen showing suppression of cells.
* Antigen supplied by Dr. Leslie Gay, Johns Hopkins Hospital.

scleral trephine. With this method as many as forty explants were rapidly prepared from one buffy coat. Each explant was placed on a separate cover glass and two drops of the bacterial filtrate were dropped directly on the explant. One drop of concentrated fibrinogen and one drop of full strength thrombin were added. As soon as the explants coagulated, the cover glasses were inverted over hanging drop slides containing Ringer's solution and ringed with vaseline. The slides were placed in a moist chamber and incubated at 37° C.

Normally the small wandering cells begin to migrate in a few hours. At twelve hours migration ceases and the cells then remain stationary and viable for periods up to four days. When migration has ceased the hundreds of cells form a dense corona around the explant with many cells scattered throughout the media. This degree of extensive cell migration was arbitrarily recorded as 4. If there are only a few scattered viable cells along the edge of the explant the test is recorded as 1. Explants surrounded by viable cells in limited numbers are recorded as 2. Designations 3 and 4 refer to the normal picture of extensive cell migration with corona formation. If the explant is completely necrotic it is recorded as 0.

EXPERIMENTAL

This report concerns itself with the results of the first fifty patients tested against the filtrates from the following bacteria: Streptococcus hemolyticus group A, Streptococcus viridans, Staphylococcus aureus hemolyticus, Staphylococcus aureus anhemolyticus, and Diplococcus pneumoniae. Forty of the patients tested showed no suppression to any of the antigens even in full strength. Six showed suppression to some of the antigens either in full strength or in dilutions of up to 1:100 while the remaining four patients all showed suppression in dilutions from 1:1,000 to 1:10,000 (Table I). These last four patients were all seriously ill and included the only two patients with rheumatoid arthritis tested thus far.

The slide cultures were retained for three days, but positive results

TABLE II. PATIENT (SK) TITERED TO H-STREPTOCOCCUS PNEUMOCOCCUS MIXED VACCINE

Antigen	Dilution	10 Hours	36 Hours	45 Hours	60 Hours
H-Streptococcus, pneumococcus mixed vaccine	1:1,000	1	0	0	0
	1:5,000	2	1	0	0
	1:10,000	3	3	3	3
	1:50,000	4	4	4	4
	1:100,000	4	4	4	4
Control	Ringer's	4	4	4	4

TABLE III. EFFECT OF DESENSITIZATION UPON THE HYPERSENSITIVITY TITER (PATIENT GD)

Antigen Dilution	Before Desensitization	After Two Months Desensitization
H-Streptococcus 1:100	0	0
1:1,000	0	2
1:5,000	0	4
1:10,000	1	4
1:50,000	4	4

could be read as early as ten hours. Occasionally when performing a titration it became necessary to keep slides for forty-eight hours. In such cases where a 1:1,000 dilution showed complete suppression and a 1:10,000 dilution no suppression, the dilution of 1:5,000 showed no change until twenty-four hours when the cells clumped and rapidly underwent necrosis. The final titer was recorded as 1:5,000 (Table II).

When specific hypersensitivity is determined, the patient may then be desensitized and subsequently retested. Desensitization may be continued until the titer level is sufficiently low and, in addition, the patient may be tested from time to time to note any return of the hypersensitive state. Table III demonstrates this value of the test. This patient had rheumatoid arthritis with recurrent uveitis in both eyes. The titer level before desensitization was 1:10,000; at the end of two months of desensitization it had dropped to 1:1,000. Although symptom-free at the present time, the patient shows a titer of 1:5,000 against a green streptococcus. As more antigens become available new tests will be performed with a view to preparing additional antigens for desensitization purposes.

DISCUSSION

The use of tissue cultures in the study of bacterial hypersensitivity is not new. Holst[2] in 1922 was the first who attempted to demonstrate a specific tissue hypersensitivity to tuberculin in the experimental animal. His failure may be attributed to his methods. Rich and Lewis,[7] however, in 1928 succeeded in demonstrating a specific toxic effect of tuberculin in high dilutions on both the splenic cells and the white cells of the buffy coat of tuberculin-sensitized guinea pigs. This reaction was entirely absent

in normal animals. These results have since been confirmed by Aronson[1] and Moen and Swift.[3] Moen was able to demonstrate the same specific necrosis of tissue cultures taken from animals sensitized to group C streptococci only when these cells were mixed with the specific antigen and not with other related strains. This effect was observed when the streptococcic antigen was diluted even to 1:6,000. Moen used splenic explants and read the test at the end of four days by comparing the rate of growth of the explant in the bacterial antigen with the rate of growth of the control. This ratio was referred to as the cytotoxic index and was invariably less than 1 in hypersensitivity and 1 or larger in normals. In attempting to correlate the results of his tests with the skin test, Moen observed that "no correlation was found between the degree of cutaneous reactivity to a given bacterial extract and the degree of sensitivity of splenic explant cells to the same extract *in vitro*."

There are two serious criticisms of the test as performed by these investigators. First, the explants do not remain viable and the cells do not migrate in the absence of plasma. Unfortunately plasma contains many properties which can interfere seriously with the sensitivity of the test. Moen states "other tissue culture studies on hemolytic streptococcic allergy indicate that immune plasma has a neutralizing effect on the toxic action of streptococcic extract when tested on sensitive cells." Consequently Rich found it necessary to combine allergic cells plus allergic plasma, allergic cells plus normal plasma, and normal cells plus allergic plasma in order to evaluate properly each individual test. This difficulty has been overcome here by the substitution of fibrin for plasma. In this fibrin matrix the small wandering cells migrate as well as in plasma. Furthermore we are not dealing with plasma precipitins and agglutinins which interfere seriously with the test. Finally, the necessity of keeping explants for four days and measuring cytotoxic indices makes the test rather cumbersome. Each test must be controlled with a separate tissue culture, and the readings are rather tedious. We found that explants placed on a hanging drop slide filled with fluid showed better cell migration than explants placed in tissue culture slides containing an air chamber. It therefore became unnecessary to make cytotoxic index determinations. The test can be read by merely a quick glance at the low power magnification. With these modifications we have found it possible to make as many as forty separate tests from a single 9 c.c. specimen of blood. The patient may thus be tested separately to many antigens or accurately titered by using various dilutions of a single antigen.

SUMMARY

Tissue culture of the patient's white blood cells in the presence of bacterial filtrates is offered as a new clinical test for bacterial hypersensitivity.

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ACTIVE SENSITIZATION TO POLLEN

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IN the course of a series of local passive transfer tests four recipients have become skin sensitive to ragweed pollen. These are four of forty-seven who served for experiments with ragweed. Only ragweed sensitizations have developed, in spite of the fact that a larger number of experiments have been done with other highly antigenic pollens such as timothy, sagebrush, pigweed and mountain cedar, involving the services of 123 recipients in all. None of the four who developed sensitization to ragweed did so to other pollens, though their exposure to them in these experiments was as great or greater.

The recipients were random volunteers selected only for their firm responsive skins and histories of freedom from pollen sensitizations. But, in common with the entire population of the community, all had suffered heavy seasonal exposure to the pollen of ragweed, and to a lesser extent to that of timothy and related grasses, in most cases for their entire lives. But none had at any time previously been exposed to the other pollens used in the experiments. It was noted that in the ragweed tests the recipients responded with irregularities which did not occur in the tests with the pollens to which they had never been exposed. A large proportion of them accepted passive transfer to ragweed-sensitive serum very poorly and several failed completely, though accepting transfer to other pollens readily enough, which suggests the presence of a blocking antibody. One reacted to the ragweed reaginic serum, leaving the sites thereafter negative to ragweed, indicating the presence of circulating ragweed antigen. Thus there is evidence that a large proportion of a population annually exposed to ragweed pollen respond to the pollen in other ways than by developing clinical sensitization to it.

CASE REPORTS

Case 1.—A woman, aged twenty-seven, gave a personal history of no allergy, except of having had hives when very young. This was believed to have been due to fish and citrus fruits though not demonstrated by skin tests. Now she eats these and all other foods without symptoms. She has no immediate family history of allergy but her brother's child has eczema from wheat and cow's milk.

She was shown by scratch test to be skin negative to ragweed, sagebrush, mountain cedar, timothy, and pigweed. Before she served in ragweed tests she had already served in experiments with sagebrush, mountain cedar and timothy, accepting passive transfer and responding normally in every way.

On September 24, 1946, she was used in a ragweed neutralization experiment receiving in all 14.3 units* of ragweed. She was proved negative to ragweed at this time by seven negative retests.

On November 19, 1946, she was again used in a ragweed neutralization experiment. At this time she was not suspected of being sensitive to ragweed but it was noticed that the transfer sites were not neutralized by the amount of ragweed

*One unit = 0.00001 mg. N.

(.0746 units) which was known to be well beyond the neutralizing potency for the serum with other recipients. It is, therefore, probable that she had some sensitization to ragweed at this time. The experiment required the injection of a total of 121 units.

On January 11, 1947, she again served in a ragweed neutralization experiment. This time she reacted to the control, 0.01 c.c. of ragweed, 1,000 units per c.c. with a wheal 5 mm. and erythema 20 mm. in diameter. Since this reaction was small and it was thought to have been influenced by strongly reacting transfer sites on the same arm, it was not interpreted as sensitization at the time. She was, however, tested again on June 3, 1947, when it was found that she gave a similar reaction of 5 and 15 mm. to 0.01 c.c. of 100-unit ragweed. This confirmed the former test on January 11.

It is uncertain whether this recipient acquired sensitization before or after November 19, 1946. If the former, it followed the injection of 14.3 units with a time lapse of less than two months; if the latter, it followed the injection of 135.3 units with a time lapse of less than four months. In either case the dosage seems strikingly small considering that an immunizing course of treatment with ragweed pollen calls for the injection of 11,680 units. The dosage value of 14.3 units is less than the third dose in the treatment series, and 135.3 is less than the seventh.

Case 2.—A woman, aged twenty-two, has mild symptoms resembling hay fever from June to September, especially in July and August. At other times is easily made to sneeze by smoke and dust. She was shown by scratch test to be negative to ragweed, pigweed, timothy and mountain cedar, but gave marked reactions to cat hair and house dust, and a border-line reaction to mixed feathers. Before she was used in ragweed experiments she had been used in timothy and Bermuda-grass experiments, and behaved normally in every way.

On September 5, 1946, she was used in a ragweed *in vivo* neutralization experiment. At this time she was shown to be nonsensitive by ten negative retests with 0.01 c.c. of ragweed, 100 units per c.c. In this experiment she received a total of 18 units of ragweed.

On October 31 she was again used for a similar ragweed experiment. In this, all but one of the retests with 1,000-unit ragweed were positive, while in an identical check experiment done on another recipient, all retests were negative except the unneutralized controls. Her sensitization was confirmed on June 3, 1947, when she responded to 0.01 c.c. of ragweed, 100 units per c.c., with a wheal of 8 and erythema of 40 mm. diameter. It would thus appear that this recipient became sensitized in two months or less after the injection of only 18 units of ragweed pollen or slightly more than the equivalent of the first two doses of the ordinary treatment schedule.

Case 3.—A woman, aged thirty-nine, has dermographia and gave a personal history of having had a severe attack of hives at the age of sixteen from eating soft-shell crabs, and again in her early thirties from the same cause. She can eat canned crabmeat and all other sea food with impunity. Her antecedent family history is negative but her one son is frankly allergic. At the age of seven to eight months he had eczema from eggs, shortly followed by asthma from the same cause. Later he developed hay fever and asthma from ragweed pollen.

The mother was shown to be negative to ragweed by scratch test. Before serving in ragweed experiments, she had been used in a timothy and a Bermuda grass experiment and responded normally.

On July 30, 1946, she served in a cross neutralization experiment, receiving a total of 36 units of ragweed. At this time she was shown to be negative to ragweed since all the ragweed reciprocals were negative.

On October 29, 1946, she served in a ragweed *in vitro* neutralization experiment. At this time she reacted to all the retests, though a substantial proportion of these should have been completely neutralized. Her sensitization was confirmed at a later date (December 17, 1946) when it was found that 0.01 c.c. of 1,000-unit ragweed endermally at a normal site produced a wheal of 11 mm. diameter and erythema of 25 mm. It thus appears that this recipient became sensitized after the injection of 36 units of ragweed, and after not more than three months.

Case 4.—A man, aged thirty-two, gave no personal history of allergy, except that working with guinea pigs caused a rash on his hands and arms which was thought to be contact dermatitis from the fur of the animals. However, both scratch and patch tests with guinea pig fur, and likewise with their food and bedding materials, proved negative. During the course of the experiments he was discovered to be skin sensitive to timothy, 0.01 c.c. of 1-unit pollen extract endermally producing a wheal of 9 mm. and erythema of 50 mm. diameter.

His family history shows that his father suffered severe asthma during the late summer months.

The man was shown to be negative by skin test to sagebrush, mountain cedar and ragweed, so was considered a suitable recipient for experiments with these antigens.

On October 18, 1945, he served in a ragweed neutralization experiment. The control tests showed that he was negative to ragweed at this time. He received a total of 12 units in this experiment.

On March 15, 1946, he served again in a ragweed *in vivo* neutralization test, receiving a total of 120 units of ragweed pollen. The retests showed him to be negative to ragweed at this time.

On September 5, 1946, he served in a tall and short ragweed neutralization experiment, receiving 48 units of ragweed in all. Retests and reciprocal tests were negative, proving him to be nonsensitive to ragweed at this time.

On November 4, 1946, he was used again in a ragweed *in vitro* neutralization experiment, receiving a total of 125 units. The retests in this experiment failed to detect any appreciable amount of neutralization indicating that the recipient was strongly sensitive to ragweed. His sensitization was not recognized at the time but was subsequently brought to attention January 8, 1947, when it was found that 0.01 c.c. of 1,250-unit ragweed gave a reaction of 10 and 45 mm. in a normal site. It is apparent that this recipient became skin sensitive following the injection of 180 units of ragweed, between September 5 and November 4, 1946, about one year after his first and two months after his last ragweed injection.

At the close of the 1947 ragweed season all four persons reported having experienced no symptoms of hay fever though they had spent the entire time in regions infested with ragweed.

On September 16 all were tested again with ragweed for skin sensitivity, using 0.01 c.c. of short ragweed, 100 standard N. units per c.c. intracutaneously. Case 1 gave a wheal of 7 and erythema of 30 mm. in diameter; Case 2, 7 and 30 mm.; Case 3, 8 and 30 mm.; Case 4, 6 and 25 mm. Case 1 shows a definite increase in sensitivity from a reaction of 5 and 15 mm. to 7 and 30 mm. from the same dose, three months earlier. Case 2 shows a slight decrease from 8 and 40 mm. to 7 and 30 mm. from the same dose three months earlier. In Case 3 and Case 4 it is not known whether the final reactions of 8 and 30 mm. and 6 and 25

mm., respectively, indicate any change in sensitivity, since their earlier doses were much larger. The reactions of 11 and 25 mm., and 10 and 45 mm., respectively, which were obtained nine months earlier were elicited by 0.01 c.c. of ragweed of 1,000 and 1,250 units per c.c., amounts which we did not feel justified in using with cases of known sensitivity. It is probable, however, that Case 4, at least, has lost some sensitization.

It is well known that the serum used in local passive transfer tests is sometimes sufficient to induce a general skin sensitization. It is hardly possible that such could have been the case with these sensitizations because of the minute quantities of sera that were used. In all, Case 1 received 0.126 c.c.; Case 2, 0.5 c.c.; Case 3, 0.09 c.c.; Case 4, 0.41 c.c. of ragweed sensitive serum. Moreover, these sensitizations have persisted for from three to nine months, whereas passive sensitizations, even those resulting from transfusions of large quantities of blood, persist but a few weeks. It is therefore inescapable that these four recipients were actively sensitized by the injection of ragweed pollen extract.

Human beings are easily sensitized by injection to certain substances such as horse serum and some of the newer drugs but to most substances which are the causes of the ordinary allergies, sensitization can be accomplished only with the greatest of difficulty or not at all. Moreover, apparently only atopic individuals respond in this way. Thus Brunner[1] (1934) attempted to sensitize fifteen people using orris root, rabbit epithelium, egg, ascaris and cat dander. Only with orris and ascaris was he successful. Orris sensitization was one out of eight attempted; ascaris was three out of five.

He concludes that it is very difficult to sensitize human beings actively by subcutaneous injections of atopens which are common and important offenders. Those who were sensitized were inherently allergic to some other substance before the attempt was made. Though people with negative personal and family histories of atopy were included in the experiment, none of them became sensitized. The sensitizations thus artificially produced contrasted sharply with spontaneous sensitizations in that they were only transitory, disappearing in from one to two years.

A perusal of the literature has failed to reveal any report of human beings becoming sensitized to pollen through injection. On the contrary, many statements are found to the effect that such is impossible. Lamson and Miller[5] (1927) put the question to a searching test. They treated, by the usual course of therapeutic injections, thirty-three allergic patients with pollens to which they were nearly or quite negative. The only indication of sensitization which they encountered was that, "There are four instances, representing four different pollens and three patients, in whom the test two weeks after treatment was considered to be more positive than before treatment, but in no case has this been shown to be the case at the last test." They conclude that, "The injection of the amount of pollen that is commonly used for treatment . . . fails to induce positive

skin reactions in allergic patients who previously have given negative skin reactions to the pollen."

These authors argue that, though a postive skin reaction to pollen or other allergen is obtained after a patient has given consistently negative reactions for a month or more, this must not be considered proof that that particular sensitization has been recently acquired. It appears, they say, that this phenomenon might be explained by assuming that the sensitization had existed for some time, but that the threshold of resistance had but recently been exceeded.

One of the principal factors in spontaneous pollen sensitization is that of time, generally years. Thus it is that in Bermuda, where the only hay fever is caused by the pollen of Bermuda cedar, Hodgson[4] (1935) tells us that it affects only permanent residents; no case has ever been recorded among the many transients. The latter are gone again before they have time to develop sensitization. Phillips[7,8] (1928, 1932) records that persons sensitive to eastern grass settling in Arizona are nearly always free from hay fever for three to five years before they have time to succumb to the effects of the pollen of Bermuda grass which is known to be antigenically different from that of the eastern grasses. The same author[9] (1939) finds that, "Two years of seasonal contact seem to have been the time required to develop clinical evidence of sensitivity to the newly encountered pollen [beet] . . . with an adequate exposure in the third year." With regard to Johnson grass smut, Phillips[10] (1940) finds that it takes at least five years of exposure before the development of positive reactions.

It appears that the time factor may be influenced to some extent by the degree of exposure. Thus Nelson[6] (1934) studying the onset of hay fever by age classes records that it takes at least a number of years of exposure to pollen to develop sensitization. But he found that a preponderance of males became sensitized during the first decade of life, while with females it was during the second and third decade because, he says, the life of a small boy leads him among pollen-producing weeds much more than that of a small girl, the greater exposure of the former causing earlier development of sensitization.

Clark and Leopold[2] (1940) added to these observations of Nelson, their findings on European-born immigrants in relation to ragweed. Coming to America from countries where ragweed is virtually absent, these immigrants require the same exposure period to ragweed pollen as native Americans. They find that immigrants develop hay fever mostly after eleven to twenty years of exposure regardless of their age upon arrival, while native Americans develop it mostly at the ages of eleven to twenty in the same environment.

Figley and Elrod[3] (1928) reported the development of asthma from castor bean dust emanating from an oil mill, among the local population of Toledo. Of these people the authors say, "None of them had asthma

before moving into this district, and the onset of attacks varied from one to seventeen years after moving into the neighborhood." Thirty patients presented themselves for study. It was found that three became sensitized during the first year of their exposure, but the majority took two to five years. Only thirteen of the thirty persons showed personal or family history of atopy. However, since this is a larger proportion than would be found among a similar group of normal individuals, the authors feel justified in saying, "We feel that our series of cases helps to support the view that asthma occurs only in persons who are hypersensitive through inheritance," attributing the discrepancy in figures to the difficulty of getting adequate histories from people of so low a social standing.

Of the four cases with which the present report is concerned three became sensitized in much less than a year and one in about a year. All had a family or personal history of atopy. Only sensitizations to ragweed developed, though there was greater opportunity for sensitization to other pollens. This latter fact and the extremely short time taken for their sensitization are evidence that all were on the road to sensitization from their natural exposure to ragweed pollen, and that the injections of the pollen served only to accomplish the last step.

The problem requires further study before definite conclusions can be drawn. However, the evidence here presented points to the conclusion that, though it is extremely difficult to sensitize human beings to pollen by injection, it can be done providing they are inherently atopic and the pollen used is one to which they are annually exposed. And the corollary to this is: for making passive transfer tests only nonatopic individuals should be used, in so far as this can be determined, and they should be drawn from a population not regularly exposed to the antigens to be tested.

REFERENCES

1. Brunner, M.: Active sensitization in human beings. J. Allergy, 5:257, 1934.
2. Clarke, J. A., and Leopold, H. C.: Effect of pollen contact upon the age of onset of hay fever. J. Allergy, 11:494, 1940.
3. Figley, K. D., and Elrod, R. H.: Endemic asthma due to castor bean dust. J.A.M.A., 90:79, 1928.
4. Hodgson, F. H.: Report of botanical survey of Bermuda. New York State J. Med., 35:(22), XXVII, 1935.
5. Lamson, R. W., and Miller, H.: Pollen allergy II, Genesis of skin hypersensitiveness in man. Arch. Int. Med., 40:618, 1927.
6. Nelson, Tell: Constitution and allergic manifestations. I, Age-Sex incidences of allergic conditions. J. Allergy, 5:124, 1934.
7. Phillips, E. W.: Ragweed hay fever in Salt River Valley. Southwestern Med., 12:49, 1928.
8. Phillips, E. W.: Pollen incidence in Central Arizona. J. Allergy, 3:489, 1932
9. Phillips, E. W.: Time required for the production of hay fever by a newly encountered pollen, sugar beet. J. Allergy, 11:28, 1939.
10. Phillips, E. W.: Time required for the production of hay fever by spores of a newly encountered fungus, Johnson grass smut. J. Allergy, 12:24, 1940.

THE EFFECT OF DRUGS IN MODIFYING THE RESPONSE OF ASTHMATIC SUBJECTS TO INHALATION OF POLLEN EXTRACTS AS DETERMINED BY VITAL CAPACITY MEASUREMENTS

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A REDUCTION in vital capacity may follow the inhalation of aerosolized extracts of pollen in certain asthmatic subjects.[6] As Brown, et al[1] have also shown, reductions in vital capacity may occur in individuals with hay fever and bronchial asthma during the pollen season. The changes in vital capacity induced by us are reproducible, and the tests need cause little or no discomfort to the subject. The symptoms and signs which may accompany the pulmonary reaction resemble naturally occurring asthma in every respect except that they are usually of short duration. If necessary, the symptoms can be relieved and the vital capacity quickly increased by the administration of a suitable drug.

The three subjects chosen for these studies exhibited high degrees of responsiveness as indicated by marked reductions in vital capacity following exposure to aerosolized pollen extracts. Not more than a single exposure to a pollen to which the patient was sensitive was made on any one day, and the subjects were not tested during periods of spontaneously occurring asthma. With the subject seated and rested, exposure was carried out by a number of deep oral inhalations from a No. 40 DeVilbiss nebulizer supplied with oxygen flowing at a rate of 6 liters per minute. Vital capacity measurements were made with a Benedict-Roth metabolism machine arranged so as to produce a tracing of the expiratory curve on a moving drum.

Pollen extracts were prepared in the proportion of 1 gm. of dry pollen to 30 ml. of extracting fluid. Tests were also made using aerosolized solutions containing histamine in a concentration of 50 mg./ml. and acetyl-beta-methyl choline also in a concentration of 50 mg./ml. No fall in vital capacity occurred in control tests done with extracting fluid alone. The subjects were observed for signs of asthma during the tests and notes were made of their subjective sensations.

The capacity of four drugs to prevent the fall in vital capacity which regularly followed five inhalations of an aerosolized extract of birch pollen was investigated. The drugs used were aminophylline given intravenously in a dose of 0.48 gm., epinephrine given subcutaneously in doses of 0.3 ml. to 0.5 ml., atropine given intravenously in doses of 0.6 mg. and 1.2 mg., and pyribenzamine given intravenously in a dose of 25 mg. Of these agents, given in the manner described, aminophylline pro-

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vided the greatest protection to the patient, both with regard to fall in vital capacity and symptoms. Epinephrine gave definite but incomplete protection whereas neither atropine nor pyribenzamine afforded any protection whatsoever. The position of pyribenzamine in the treatment of asthma is still unclear, but there is a general agreement that this drug rarely gives prompt relief of the asthmatic attack. Atropine likewise is usually ineffective. These results, therefore, are in keeping with clinical experience and indicate that this method of investigation may provide a useful means of assaying the effectiveness of new drugs for the treatment of asthma.

Another series of tests were carried out to determine whether the vital capacity, once reduced as a result of inhalation of a pollen extract, could be restored by the administration of various drugs. It was found again that aminophylline was superior to the other drugs in this respect. Epinephrine given subcutaneously in doses of 0.3 ml. and 0.5 ml. was likewise effective but less so than aminophylline.. A number of tests were done with Isuprel* (1-(3^1, 4^1-Dihydroxyphenyl)-2-isopropylamino ethanol) in a concentration of 0.5 per cent. This was administered with the nebulizer in the same manner as the pollen extracts. Five deep inhalations of this solution was usually sufficient to increase the vital capacity markedly when this had been lowered by inhalation of a pollen extract. This preparation, administered in this manner, was more effective than subcutaneously administered epinephrine in the dosage used, but less effective than intravenously administered aminophylline. Atropine and pyribenzamine, both of which were given intravenously, were entirely without effect in restoring the vital capacity after this had been decreased by inhalation of pollen extract.

Tests were performed to determine the effect of pyribenzamine or atropine in preventing or relieving the reduction in vital capacity which could be readily produced in our subjects by exposure to aerosolized solutions of histamine or acetyl-beta-methyl choline (Mecholyl). The tests were similar to those described by Curry[2,4] and Curry and Lowell[5] in which histamine and Mecholyl were given parenterally. It was readily shown that atropine decreased the response to inhaled Mecholyl but pyribenzamine was without effect. In contrast to the results in the pollen tests, pyribenzamine gave complete protection against inhaled histamine and also restored the vital capacity when this had been lowered by inhalation of histamine. This result indicates in all probability that the failure of pyribenzamine to protect the subjects against the effects of inhaled pollen extracts was not due to the manner or dosage in which it was administered, and provides an argument against the hypothesis that histamine release is a determining factor in the production of the pollen-induced asthmatic attack.

*Supplied by courtesy of Frederick Stearns and Co.

SUMMARY

Measurement of changes in vital capacity was used as a means of studying the effect of various drugs in modifying the response of three asthmatic individuals to the inhalation of aerosolized pollen extracts, and to solutions of histamine and acetyl-beta-methyl choline. The results indicate that the method is a useful one for the study of bronchial asthma. The failure of atropine and pyribenzamine to influence the pulmonary response to inhaled extracts of pollens suggests that neither acetylcholine nor histamine are determining factors in the production of the pollen-induced asthmatic attack.

REFERENCES

1. Brown, E. A.; Nobili, C.; Sannella, T., and Wadsworth, G. P.: Dyspnoea and diminished vital capacity as a symptom and a sign in hay fever. Dis. of Chest, 12:3, (May-June) 1946.
2. Curry, J. J.: The action of histamine on the respiratory tract in normal and asthmatic subjects. J. Clin. Investigation, 25:785, (Nov.) 1946.
3. Curry, J. J.: The effect of antihistaminic substances and other drugs on histamine bronchoconstriction in asthmatic subjects. J. Clin. Investigation, 25:792, (Nov.) 1946.
4. Curry, J. J.: Comparative action of acetyl-beta-methyl choline and histamine on the respiratory tract in normal patients with hay fever and subjects with bronchial asthma. J. Clin. Investigation, 26:430, (May) 1947.
5. Curry, J. J., and Lowell, F. C.: Measurements of vital capacity in asthmatic subjects receiving histamine and acetyl-beta-methyl choline. A clinical study. J. of Allergy (in press).
6. Lowell, F. C., and Schiller, I. W.: Reduction in the vital capacity of asthmatic subjects following exposure to aerosolized pollen extracts. Science, 105:317, (March 21) 1947.

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5. Duke, W. W.: Asthma, Hay Fever, Urticaria, and Allied Manifestations of Allergy. Ed. 2. St. Louis: C. V. Mosby, 1926.
6. Fink, H. W.; Burton, I., and Wheeler, W. E.: The applicability of skin tests for sulfonamide hypersensitivity in children. J. Immunol., 54:65-67, 1946.
7. Gay, L. P.: Gastrointestinal allergy. J.A.M.A., 106:969-976, 1936.
8. Kenedy, D.: Gior. ital. di. dermat. e sif., 75:965, 1934.
9. Landsteiner, K.: The Specificity of Serological Reactions. Springfield, Illinois: Charles C Thomas, 1936.
10. Landsteiner, K., and Jacobs, J.: Studies on the sensitization of animals with simple chemical compounds, II. J. Exper. Med., 64:625-639, 1936.
11. Leftwich, W. B.: An intradermal test for the recognition of hypersensitivity to the sulfonamide drugs. Bull. Johns Hopkins Hosp., 74:26-48, 1944.
12. Long, M., and Der, O.: Gelungene Passive Webertragungsversuche bei Arznei-idiosynkrasien. München. med. Wchnschr., 74:59-60, 1927.
13. Oriel, G. H.: Some observations on the pathogenesis of eczema of internal origin and other allied diseases. Proc. Roy. Soc. Med., 24:1171-1180, 1931.
14. Walzer, M.: Studies in absorption of undigested proteins in human beings. J. Immunol., 14:143-174, 1927.

Reports in Brief

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FAILURE OF CERTAIN HISTAMINE-LIKE SUBSTANCES TO PRODUCE OR TO INHIBIT WHEALS IN THE HUMAN SKIN

Preliminary Report

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PRIOR to 1942 experiments were performed with Dr. R. K. Lambert and with Dr. H. T. Clarke on the pharmacology of histamine-like substances on the eye and skin of man. Table I briefly summarizes the data available. In the intradermal tests mixtures were made and injected together intradermally. The volume of the injected material was between 0.03 and 0.05 c.c. In the eye, the inhibiting substance was permitted to act for several minutes before the histamine was introduced. Pertinent references on the general problem of the relationship on the spatial configuration of histamine-like substances to the problem are appended.

Of particular interest is the fact that imidazole methylamine does not produce a wheal in high concentration. Nor does it protect against intravenous histamine. More important, perhaps, would be similar studies with imidazole propylamine. Many of the compounds listed in Table I produce whealing due to irritation if they are not brought to pH 7.4. It was most surprising to see that 1 per cent ethylamine brought to pH 7.4 may be safely put into the eye without irritation. The reported wheal production by histidine was not observed in a suitably buffered solution. Evidently many histamine-like substances, especially imidazole, methyl imidazole and imidazole methylamine (protohistamine), neither reproduce the whealing response of histamine in the human skin nor do they readily inhibit the histamine reaction. Findings contrary to those reported here for histidine, allantoin and urea are in the literature.

References

1. Ackermann, D., and Wasmuth, W.: Zur Kenntniss der Beziehung des Histamins zum anaphylaktischen Schock. Ztschr. physiol. Chemie, 260:155, 1939.
2. Ackermann, D., and Wasmuth, W.: Zur Wirkungsweise des Histamins. Ztschr. physiol. Chemie, 259:28, 1939.
3. Edelbacher, S., Jucker, P., and Baur, H.: Die Beeinflussung der Darmreaktions des Histamins durch Aminosäuren. Ztschr. physiol. Chemie, 247:63, 1937.
4. Landau, S. W., and Gay, L. N.: Influence of certain amino acids on histamine reactions and anaphylactic reactions. Bull. Johns Hopkins Hosp., 74:55, 1944.
5. Silva, M. R. E.: Inhibition of histamine effects by compounds of histamine, histidine and arginine. J. Pharm. Exp. Ther., 80:399, 1944.
6. Winkenwerder, W. C., Buell, M. V., and Howard, J. E.: The sensitizing properties of nucleic acids and their derivatives. Science, 90:356, 1939.

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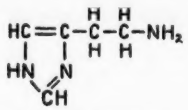
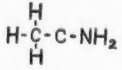
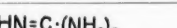
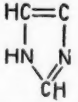
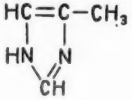
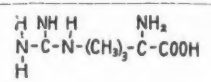
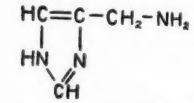
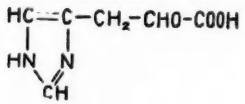
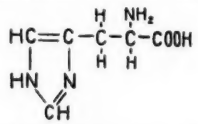
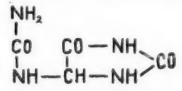
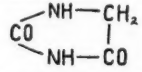
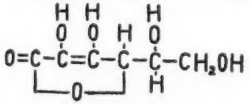
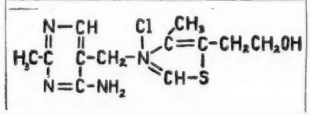
From the First Medical Service and the Laboratories of the Mt. Sinai Hospital, New York City.

TABLE I. FORMULA FOR HISTAMINE



	Compound or Mixture	Name	Conc.	Tissue	Histamine-like Reaction	Inhibition of Histamine
1.		Ethyl amine phosphate (pH 7.4)	1.0%	Eye	None	None of 1:1,000
			0.1%	Intradermal	None	None of 1:50,000
2.		Guanidine	1.0%	Intradermal	None	None of 1:1,000,000 Histamine
3.		Imidazole at pH 7.4	2.0%	Eye	None	None of 1:1,1000
				Intradermal	None	None of 1:50,000
4.	Mixture of Imidazole and Ethyl amine at pH 7.4		1.0% 0.75%	Eye	None	None of 1:1,000
				Intradermal	None	None of 1:50,000
5.		Methyl Imidazole at pH 7.4	1.0%	Intradermal	None	No inhibition of 1:50,000 histamine
6.		Arginine	0.5% at pH 7.4	Intradermal	None	None of 1:50,000. None of 1:10,000 by electrophoresis also.

7.		(Protohistamine) Imidazole methyl amine at pH 7.4 prepared by Prof. H. T. Clarke.	0.1%	Intradermal	None	No inhibition in mixture by 1:2,000 protohistamine of 1:200,000 histamine. No protection against intravenous histamine.
8.		Imidazole Lactic Acid pH 7.4	0.5%	Intradermal	None	No inhibition of 1:50,000
9.		Histidine Histidine at pH 7.4	2.5% 0.5%	Eye Intradermal	None None	None of 1:1,000 None of 1:50,000 None of 1:10,000 by electrophoresis
10.		Allantoin	0.5%	Intradermal	None	No inhibition of 1:50,000 histamine
11.		Hydantoin	0.5%	Intradermal	None	No inhibition of 1:50,000 histamine
12.		(Ascorbic acid) Vitamin C	1.0%	Intradermal	None	No inhibition of 1:50,000 histamine
13.		(Thiamin) Vitamin B_1	0.6%	Intradermal	None	No inhibition of 1:50,000 histamine

PHARMACOLOGY OF A NEW BRONCHOCONSTRICTOR DRUG, HEXAETHYLTETRAPHOSPHATE

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BRONCHIAL spasm and other symptoms of parasympathetic excitation may be elicited by acetylcholine, cholinotropic agents such as pilocarpine or arecoline, and by drugs that prevent the destruction of acetylcholine by cholinesterase, the so-called cholinesterase inhibitors or anticholinesterases. A new and highly effective insecticide, hexaethyltetraphosphate, and probably a number of other similar compounds as yet not investigated from the standpoint of their antiesterase activity belong to the latter group.

The pharmacology of this new bronchoconstrictor, hexaethyltetraphosphate (HETP), has been studied in anesthetized dogs and curarized rabbits. Since this substance is a cholinesterase inhibitor it is expected to potentiate the effects of intravenously injected acetylcholine as well as effects following faradic stimulation of parasympathetic nerves. This is, indeed, the case, for hexaethyltetraphosphate in doses of from 0.1 to 0.2 mg. per kg. potentiated the vasodepressor, bronchoconstrictor and other effects of acetylcholine or converted ineffective doses of acetylcholine into effective ones. The same is true of peripheral vagus stimulation, which is markedly potentiated by HETP. This anticholinesterase is capable of exerting intense parasympathetic stimulating effects also without a previous or subsequent acetylcholine administration; a dose of HETP of 1 mg. per kg. being almost immediately fatal in an anesthetized dog due to bronchial spasm and cardiac arrest. However, since doses of HETP of from 0.1 to 0.3 mg. per kg. produce no independent parasympathetic effects when administered alone, the margin of safety for this substance appears to be narrow.

Large doses of acetylcholine in atropinized animals are capable of stimulating autonomic ganglia and skeletal muscle. This effect, otherwise known as the nicotinic effect of acetylcholine, is potentiated by HETP. Doses of acetylcholine ranging from 0.0005 mg. to 0.05 mg. per kg., which in atropinized animals never produced a rise in blood pressure or other signs and symptoms of sympathetic ganglionic stimulation, are pressor in nature following premedication with HETP. To illustrate, a dose of 0.025 mg. per kg. of acetylcholine which produces no effect in atropinized animals produced a rise in blood pressure of over 100 mm. Hg. following 0.25 mg. per kg. of HETP. The optimum dose of HETP for the potentiation of acetylcholine pressor effects is about 0.25 mg. per kg. Doses larger than that do not appear to increase the magnitude of the acetylcholine pressor effect.

The anticholinesterase action of HETP suggested its use as a possible antidote in curare poisoning. A dose of 0.2 mg. per kg. of HETP administered two to six minutes before curarization with a lethal dose (2 units per kg.) of d-tubocurarine chloride saved the life of the poisoned rabbits. However, this dose of HETP was not capable of preventing ataxia, respiratory depression and partial muscular paralysis with collapse, from which the animals recovered in about an hour. With larger doses of HETP (0.3 to 0.4 mg. per kg.) administered prior to curarization the animal did not collapse. In one case HETP administered one minute after curarization also antagonized the effect of the lethal dose of d-tubocurarine.

The comparison of hexaethyltetraphosphate with other anticholinesterases reveals that it resembles more closely the reversible inhibitor of the physostigmine type than the irreversible inhibitor of the diisopropylfluorophosphate (DFP) type. The antiesterase activity of HETP is greater than that of DFP, the minimum effective dose for the elicitation of acetylcholine pressor effects being 0.05 mg. per kg. and 0.5 mg. per kg., respectively.[2,3] The smallest doses exerting maximum effects appear to differ even more widely (0.25 mg. per kg. of HETP as against about 15 mg. per kg. for DFP). The range of effectiveness of HETP is, however, quantitatively comparable to that of physostigmine. It should be noted that a recent publication[1] shows the effectiveness of HETP on the cholinesterase inhibition *in vitro* and *in vivo* and states that (a) it is more powerful than DFP, (b) that the slopes of curves for *in vitro* inhibition of cholinesterase are similar for HETP and DFP, and (c) that DFP has a longer duration of action than HETP. The above experiments confirm the first conclusion of this report.

References

1. DuBois, Kenneth P., and Mangun, George H.: Proc. Soc. Exp. Biol. & Med., 64:137, 1947.
2. Koppanyi, Theodore, Sperling, Frederick, and King, Theodore O.: Anat. Rec., 96:5, 1946.
3. Sperling, Frederick, Karczmar, Alexander G., King, Theodore O., and Koppanyi, Theodore: Fed. Proc., 6:373, 1947.

THE USE OF THE RESPIRATORY ENZYME, CYTOCHROME C, IN DYSPNEA

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BASED on the observation that the dyspnea noted in some patients with emphysema seemed greater than would be expected from their vital capacity, it was argued that injections of the respiratory enzyme, Cytochrome C, might enable them to effect more rapid absorption of the

oxygen in inspired air; both for these patients and perhaps also those with bronchial asthma. Five patients were given 10 c.c. of Cytochrome C intravenously at daily intervals for ten days. They were purposely chosen to represent each of the following categories: bronchial asthma due to inhalant sensitivities with no obvious emphysema; bronchial asthma due to inhalant sensitivities with obvious emphysema; bronchial asthma associated with chronic bronchitis, pansinusitis and moderate emphysema with no sensitivities; chronic bronchitis with emphysema associated with wheezing; and coronary heart disease with typical clinical history and electrocardiographic changes.

The patient with chronic bronchitis and emphysema was greatly improved and has had no recurrence of wheezing or dyspnea for eight months. The patients with chronic bronchitis showed less improvement. The patient with coronary disease has also resumed full activity with no anginal pains on exertion. The two patients with inhalant sensitivities, with or without infection and slight or moderate emphysema, showed no lasting improvement beyond the slight temporary, and perhaps "tonic," effect for several weeks.

Work in progress includes studies for a larger group, including other clinical conditions associated with tissue anoxia. Skin test studies on more than 200 patients have shown no incidence of postive skin reaction or any signs of allergenic sensitivity for the extract, although it is prepared from beef heart.

2-METHYLAMINOHEPTANE (OENETHYL) AS AN AID IN THE DIAGNOSIS AND THERAPY OF HEADACHES ASSOCIATED WITH HYPOTENSION

A Preliminary Report

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SINCE many patients with hypotension are asymptomatic, the possibility of cephalalgia from this cause is often not considered. Disappearance of the headache on elevating the blood pressure is the crucial diagnostic point. Heretofore, available (aromatic) vasopressors when used in amounts sufficient to effect a significant rise are accompanied by unpleasant side reactions such as nausea, precordial distress, tachycardia, tremor, nervousness, perspiration, et cetera. These are usually so objectionable and confusing to the patient that he is unable to give an unequivocal answer as to the relief of headache.

Oenethyl* 2-methylaminoheptane, is an aliphatic sympathomimetic amine with a marked and persistent vasopressor action accompanied in

*Supplied through the courtesy of the Bilhuber-Knoll Corp., Orange, N. J.

less than 10 per cent of cases with any other significant clinical manifestations. Divided doses of 5 to 10 mg. are given slowly intravenously with a continual check on the blood pressure up to a total of 25 to 50 mg., sometimes followed by an intramuscular dose of 50 to 75 mg. to obtain a prolonged effect. The disappearance of the "hypotension" headache is usually noted within three to four minutes, concommitantly with the rise in pressure. The more depressed the original blood pressure, the more notable the effect.

Hypotension is so common among allergic individuals that the term "vagotonic" is often used to described the group. Since many patients with migraine and headaches secondary to allergic rhinosinusitis may also have more or less constant dull headaches associated with hypotension, it is important for the clinician to evaluate and if possible control this latter factor.

PARENTERALLY INDUCED DRUG REACTIONS

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Roscoe, California

DRUG allergy may be divided into an atopic type and an acquired type. Sensitivity may be induced by inhalation, ingestion, contact with or parenteral injection of a drug. Regardless of mode of sensitization, parenteral injection may induce the allergic reaction. Excepting patch tests, skin tests to drugs are usually negative. Nevertheless, the responsibility of injections is the doctor's; patch or intradermal tests with non-irritating drugs are warranted, especially for common offenders like pituitrin, insulin, penicillin, liver extract, vitamin B complex and the arsenicals. Parenterally induced reactions are those common to drug allergy, i.e., fever, skin eruptions, arthralgia, et cetera, with the added danger of anaphylactic type reactions which may prove fatal.

Three reactions are reported. The first occurred after a pituitrin injection in postpartum bleeding, and consisted of pruritus, tachycardia, tremors, urticaria and angioneurotic edema. Vasomotor rhinitis was diagnosed previously with negative skin tests. Intradermal and passive transfer tests to pituitrin were negative. The second reaction occurred in a woman with arthritis after injections of Vitamin D in sesame oil. It was characterized by a painful indurated erythematous area at site of injections, an Arthus reaction. Family history positive for allergy was negative in the patient except for upset stomach from sesame. Two years later, the patient developed pollen asthma. Skin tests to sesame oil were positive but the oil had whealing properties. The third reaction occurred in a woman sensitized years before to butesyn picrate. Injection of zylecaine containing butesyn, for rectal itch, resulted in vesiculo-papular rash, angioneurotic edema and

fever. Skin tests were negative for procaine, peanut, and benzyl alcohol found in Zylecaine. Patch test to butesyn picrate gave marked delayed reaction.

METRORRHAGIA DUE TO ALLERGY TO COLD

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SYMPTOMS of physical allergy are thought to be mediated through the action of histamine. Histamine stimulates the human uterus resulting in strong contractions. It is not improbable, if unusual, therefore, that an allergy to cold, should result in uterine bleeding.

A young woman, aged sixteen, white, virginal, began menstruating regularly at twelve. In April, 1946, she began swimming in the cold school pool twice weekly. Each swim resulted in uterine bleeding lasting ten hours, never accompanied by symptoms of shock. A vacation from swimming meant freedom from bleeding.

Personal and family history were negative for allergy. Physically, the girl was normal. An intradermal test for histamine sensitivity was negative. A thirty-minute cold bath at home resulted in uterine bleeding. Histamine, 0.4 mg., was injected subcutaneously. Uterine bleeding lasting an hour started one and one-half hours later. Simultaneously with histamine desensitization injections, graduated soaking of the hand in cold water was tried, starting with one minute. After four days she had reached five minutes of inundation, and uterine bleeding started lasting twenty minutes. Shortly, thereafter, she had a normal period, after which she could soak her hands up to twenty minutes without bleeding.

She returned for treatment after swimming for the first time in three months. Her metrorrhagia had returned. She has not been seen since.

There were no blood or endometrial studies performed in this case. The fact that directly after her period the patient could relatively tolerate cold suggests that a secretory phase of the endometrium was necessary to complete the allergic reaction.

INSTRUCTIONAL COURSE ABSTRACTS AVAILABLE

A complete set of forty-five comprehensive abstracts of the lectures, with illustrations, delivered at the Cincinnati Fall Instructional Course is now available. The supply is limited. Complete set, $10.00. Orders should be addressed to American College of Allergists, 423 La Salle Medical Building, Minneapolis 2, Minnesota.

Editorial

THE PRESENT STATUS OF CERTIFICATION

On March 1, 1943, the American College of Allergists, Inc., was incorporated to "establish an organization of qualified physicians and scientists who shall meet for the purpose of promoting and advancing the study, research and clinical knowledge of allergy as it applies to the various specialties in medicine; to maintain and advance the highest possible standards among those engaged in the practice of allergy; to perpetuate the best traditions of medicine and medical ethics; to establish standards for the qualification, and procedures for the certification, of men engaged in the specialty of allergy; to maintain the dignity and efficiency of this specialty in its relation to public welfare; to promote friendly intercourse among those engaged in the practice of allergy."

In less than five years the membership of the College has increased to over seven hundred. Its roster contains many outstanding allergists noted for their accomplishments in both the investigative and clinical fields of allergy and allied subjects. A relatively large number of this group are certified by the various Specialty Boards, a representative group are sub-certified in allergy, and many occupy important positions in teaching institutions and on the staffs of our accredited hospitals.

An intensive educational program has been executed by the College, including an official publication, the ANNALS OF ALLERGY, the holding of annual meetings of a highly scientific nature, the conducting of intensive instructional courses in allergy under the auspices of accredited medical schools throughout the United States, the establishment of research fellowships, visiting clinics, and a Speakers Forum.

It was natural, therefore, that the time had come when autonomy in allergy should be recognized. In 1945, the American Society of Certified Allergists was established as a division of the American College of Allergists, Inc. This now has a membership of about 120, who compose the Founders' Group. This group was selected by a board of allergy specialists, certified by their respective boards, sub-certified in allergy, and in addition recognized by their colleagues as physicians meeting the great trust and responsibility for choosing a Founders' Group. With the exception of a few allergists who had practiced allergy for ten years or over and who have furnished evidence of research in allergy, publications on the subject and other essential requirements, all composing this group had been certified by their respective Specialty Boards.

The standards have been considerably raised and require a knowledge of allergy greater than that demanded by the committee on sub-certification in allergy. The College has conscientiously endeavored to meet all of the

requirements necessary for proposal to the Advisory Board for Medical Specialties and to the Council on Medical Education and Hospitals of the American Medical Association.

The American College of Allergists, therefore, has formally proposed to the Advisory Board for Medical Specialties and to the Council on Medical Education and Hospitals of the American Medical Association for their official approval of an American Board of Allergy.

Efforts by the College in this direction have been supplemented and encouraged by a resolution passed by our contemporary society, the American Academy of Allergy, at the business meeting of their fourth annual meeting in St. Louis, December 15, 1947, to the effect that a committee be appointed to make a similar proposal within thirty days for the establishment of an American Board of Allergy to the Advisory Board for Medical Specialties and to the Council on Medical Education and Hospitals. The favoring of an American Board of Allergy by the American Academy of Allergy reverses its hitherto approved policy of sub-certification in allergy. With the high standards maintained by both the College and the Academy, this represents a step toward proper recognition of allergy as a distinct and separate specialty as it applies to the various specialties in medicine.

F. W. Wittich, M.D.
Secretary-Treasurer, American College of Allergists

THE PRESENT STATUS OF CERTIFICATION

The American College of Allergists was incorporated in the State of Minnesota on March 1, 1943. One of the motivating purposes of the corporation clearly stated in its charter is that it is legally empowered to establish standards for the qualification and procedure for the certification of men engaged in the specialty of allergy. This was accomplished through the American Society of Certified Allergists and its independent American Board for the Certification of Allergists, both divisions of the College. These divisions were formed in January, 1946, and are still active. The reason for activating these divisions then was based upon the unmistakable need and wish of the majority of the physicians practicing allergy as a specialty.

Our aims and ideals on certification were announced in the January-February, 1946, issue and in the November-December, 1946, issue of the Annals of Allergy. To quote one pertinent and timely statement, "We hope that the Advisory Council of the American Specialty Boards will accept in our favor the logic of the situation as it is. All we did for allergists is what the majority of allergists wanted—autonomy in the matter of certification. . . . Reconciliation of a Board for the certification of allergists as an autonomous Board within the framework of the Advisory Board on Medical Specialties is a just solution and the problem should not be too difficult to resolve. It is a task worth accomplishing since the

alternatives are in disharmony with the needs of American Allergy." We continued to remain steadfast to the proposition that if allergy is to survive as a specialty, it can do so only as an autonomous specialty.

With the passing of each month, increasing numbers of allergists throughout the country have joined the crusade to practice allergy as a dignified specialty. With such support, the American College of Allergists grew and the American Society of Certified Allergists has well over 100 members who are representative of American allergy in its finest phases.

Now that the majority of the allergists in America are enlisted in support of an autonomous Board of Allergy and since it is clearly stated in the above mentioned issues of the ANNALS OF ALLERGY that the creation of our independent American Board for the Certification of Allergists was a means to an end, and in no way could be construed as a movement in defiance of "organized medicine," we, in the American College of Allergists have every reason to remain loyal to the allergists of America and will continue to labor unstintingly for autonomy in certification of allergists.

The editorial in the *Journal of the American Medical Association* outlined the steps for an application for an Allergy Board. In December, 1947, the American College of Allergists and its affiliate, the American Society of Certified Allergists, formally applied to the Advisory Board for Medical Specialties of the Council on Medical Education and Hospitals of the American Medical Association for the formation of an autonomous American Board of Allergy.

We have been patient a long time. The moment has come to implement in favor of an autonomous Board of Allergy within the framework of the American Medical Association.

Meantime, we note that our contemporary, the American Academy of Allergy, during the business session of the meeting held in St. Louis, Missouri, December 15 to 17, 1947, adopted a resolution to make formal application to the Advisory Board for Medical Specialties for an autonomous American Board of Allergy. This action, along with the previous similar action of the American College of Allergists, unites an unmistakable majority of American allergists in support of an autonomous Board of Allergy.

The American Society of Certified Allergists, an autonomous society, and the only society of certified allergists, invites all allergists who are not now members and who have been certified in allergy to become members. Your interests as certified allergists can be best served and protected by uniting with your fellow colleagues who are certified.

Remember that the specialty of allergy can only endure as a dignified specialty if it is an autonomous specialty practiced by allergists who are united in purpose and meet each other in harmony and respect. We have made a start. Let us keep it that way for all time.

M. MURRAY PESHKIN, M.D.
Secretary-Treasurer, American
Society of Certified Allergists

Progress in Allergy

DERMATOLOGIC ALLERGY

RUDOLF L. BAER, M.D., F.A.C.A., and MORRIS LEIDER, M.D., F.A.C.A.
New York, New York

This review of progress on dermatologic allergy for the past year (about July, 1946, to date) is not complete in the sense that every published item on the subject has been examined, listed and commented upon. However, an attempt was made to examine most articles in the available literature and those that seemed most significant were selected for more extended treatment. The subject matter has been divided into arbitrary topics merely as a convenient device for discussion, and to indicate those topics which at the moment seem to present the best opportunities for further study and progress.

THE GENERAL THEORY OF ALLERGY AND OF THE ALLERGIC MECHANISM

In these first postwar years, when research and study are being resumed at accustomed peacetime pace and without the peculiar selection necessitated by the war period, it appears important to the progress of allergy that one reconsider the present definitions of the term "allergy." The tendency of recent years has been to mistakenly equate allergy with hypersensitivity and with certain disease processes only and at that with diseases of sometimes complicated diagnostic routines or uncertain therapeutic possibilities. The allergic state as a desirable and clinically beneficial transformation is hardly considered or presented at all. At the same time this narrowing of the concept of allergy in some quarters is matched with a naïve avidity on the part of the general lay public for ready explanation of all disease by "allergy," on a part with such trite explanations like "acid in the system," "nerves," et cetera. Thus the word allergy in the popular mind has come to be almost synonymous with "dislike." People say they are allergic to strawberries and to mothers-in-law, to mention but two popular allergens. It has even been said that some physicians have become allergic in this sense to allergy.

Several recent articles and textbooks deal with basic concepts and formulations of the theory of allergy. It is unfortunate that some experimentalists and theoretical immunologists have narrowed the concept of allergy in a way which tends to mislead the practicing allergist in the matter of the interpretation of the phenomena of allergy. Needless to say, it is not necessary to dispute the facts gleaned from the laboratory in order to disagree with the way these facts are integrated into working theories. Often it is not a question only of who is right or wrong; rather, who has the most logical and fruitful approach.

Some workers tend to make allergy equivalent to conditions of hypersensitivity, i.e., conditions of clinical allergic disease, and do not include conditions of clinical cure or prevention and prophylaxis of disease that are of exactly similar mechanism. It is unfortunate that some practicing allergists who are concerned with effecting cure and prophylaxis of allergic disease should follow these limited formulations and thus fail to see that hyposensitivity and immunity as allergically derived conditions, naturally occurring or therapeutically induced, are equally or perhaps even more important to explore and include in allergy.

To be specific, what is allergy? Let us set down some representative definitions. Topley and Wilson,[85] representing the thought of immunologists, write: "The term *allergy* is almost impossible to define. Here we are using it in a

loose, but widely accepted sense to cover a group of reactions characterized by a heightened or accelerated (clinical?—Ed.) response to a particular type (what particular type?—Ed.) of antigen, irrespective of the balance of harm or benefit that the altered response confers on the allergic host." Other texts on immunology, e.g., by Gay, Zinsser and Kolmer, define allergy as hypersensitivity with even less qualification. Landsteiner,[48] as an example of the experimentalists's view, relegates the definition of allergy to a footnote which reads as follows: "Hypersensitivity in man is often distinguished by the name of 'allergy' but this term—originally meaning increased as well as diminished reactivity (Pirquet)—is also applied to hypersensitivity in general, usually with the exclusion of typical, anaphylaxis." Feinberg,[27] a clinician, states: "Allergy, in its broad implication, designates hypersensitiveness in man and evidences itself by abnormal responses of tissues to physical or chemical stimuli." Tuft's[86] and Cooke's[16] books express nearly the same idea. Rich[68] represents a school of thought which would like to dispense entirely with the word allergy for the reason that it has become "debauched," to use Rich's expression. Within the vagueness of these definitions, we gather that allergy is, by and large, taken to mean clinical hypersensitive states.

Others conceive of the allergic state as any pathologic clinical condition wherein antigen-antibody interaction can be demonstrated and proved causative. Where antigen-antibody interaction is not yet proved in cases of indisputable hypersensitivity, it is conceded, or presumed, that ultimately an antigen-antibody reaction will be demonstrated. Thus Doerr[22] concludes: "It seems to me permissible, when the demonstration of an antibody is not possible, or not constantly possible, to take refuge in the consideration that the (allergic) phenomena observed in both man and animals cannot be explained in any other way than by the supposition of a *pathogenic*† antigen-antibody reaction." Here we see that two of the cardinal tenets of allergy according to this concept are pathogenicity and antigen-antibody reaction. Boyd[12] follows this formulation. He defines immunity as resistance whereas allergy is hypersensitivity. All this is done despite the fact that the data presented by some of these authors themselves show that the mechanisms of immunity and hypersensitivity (their allergy) are parallel and comparable.

It seems obvious that there must be a generic word to describe both phenomena of immunity and hypersensitivity when either develops and persists by similar mechanism no matter what "the balance of harm or benefit the altered response confers on the allergic host." That word is allergy. To reduce its meaning to the level of hypersensitivity is restrictive. It removes the special connotations of "altered" and of "specifically acquired" which are inherent in the word allergy and add to hypersensitivity the quality of "specificity" which is not inherent in that word. Making allergy generic for both specifically acquired immunity and hypersensitivity permits a better understanding of certain immunizing procedures as beneficial allergic changes. Moreover, it does not prejudice clinical hypersensitivity as being necessarily harmful.

The reviewers adhere to the original concept of allergy as formed by von Pirquet[89] and Schick, and as interpreted by Sulzberger,[79] which in its simplest and most inclusive form defines allergy as any specifically acquired alteration in the capacity of living tissue to react to a substance, which substance may be animate or inanimate. In another connection[52] the following clarifying qualifications have been added to this definition: The words "alteration" and "specifically" connote (1) that the new capacity to react is ordinarily relatively constant and lasting and is always characteristically different, clinically or by laboratory evidence, from the original capacity to react; (2) that the new capacity to react may be clinically greater

†Our italics.—EDITOR.

or less than originally; (3) that the new capacity to react is in some essential way dependent upon an original or previous exposure to the same or an immunologically related substance; and (4) that the new capacity to react becomes manifest upon re-exposure only to the same or an immunologically related agent. Two other helpful criteria[79] may be added as follows: (1) the development of allergic states is characterized by a fairly constant incubation period which is, in most instances, between five days and three weeks no matter what the form of the new capacity to react; and (2) the elicitation of the several types of allergic states is attended by a characteristic reaction time, depending in character upon the type of allergic state induced or present.

We believe that this primary definition with its addenda is more flexible for inclusion under one head of a large volume of seemingly unrelated, but immunologically very definitely related clinical and laboratory phenomena. It provides a unitary theory explaining certain responses of the organism to foreign substances on the basis of the nature of the response rather than on the nature of the substances themselves or teleology with reference to the organism involved. A better terminology and language of communication can be built up from a concept wherein both hypersensitivity (often leading to clinical disease but sometimes beneficial) and hyposensitivity or immunity (often leading to nonoccurrence of disease or at least an attenuated form of disease but sometimes harmful) are included under the one head of allergy and considered as opposite poles of specifically altered reactivity.

The terms sensitivity, hypersensitivity (hyperergy), hyposensitivity (hypoergy), anergy (insensitivity), et cetera, are in themselves descriptions which imply a point of reference that is comparative. The proper way to employ the words hypersensitivity, hyposensitivity and normergy is by qualification of each when used by the adjectives allergic or nonallergic. The rest of the language of immunology may thus properly be converted for use in allergic connotations when indicated, or left for use in nonallergic senses when that is proper. To insist on pathogenicity as a hallmark of allergy amounts to removing immunity from the field of study of allergy and destroys continuity in research and understanding. That this was not intended by those who were imaginative enough to originate the concept of allergy[89] is shown by the fact that the hypersensitivity as well as the immunity after smallpox were cited as characteristic examples of allergy. To insist further upon demonstration of an antibody as proof of an allergic state at this stage of development of the subject is to cast out a large number of disease entities, *particularly dermatoses,* which clearly fulfill every other criterion of allergy, even in the limited sense of the experimentalists. However, it must be admitted that the concept of the presence of as yet undetermined antibodies in these disease entities is logical and fruitful.

Once the problem of how the theory of allergy is most correctly formulated is agreed upon, then discussions like that of Hooker[43] become understandable and meaningful. Hooker's paper reviews the contributions of Landsteiner, with proper panegyrics to their brilliance, and shows how the chemo-physical properties of haptens, antigens and antibodies, the characteristics of colloid behavior, the spatial arrangements of globulin molecules and the lattice theory of antigen-antibody interaction explain much of allergic behavior. Revealing work along these lines following clinical leads and furnishing in return clinical clues, in a ceaseless to and fro catalysis of observation and experimentation, is what may be expected as the pure sciences are applied more and more to the field of dermatologic allergy.

In a similar way, Miller and Campbell[59] interpret experiments to support a theory that reagin antibodies are peculiar and different from "normal" antibodies in that they are the result of a distorted or incomplete antibody-forming mechanism, i.e., reagins are characterized by unipolar combining groups and therefore have dif-

ferent clinical and laboratory characteristics, e.g., (1) they are heat labile; (2) their formation depends on an inherited disposition; (3) they do not produce precipitate with specific antigen; (4) they are skin sensitizing, and (5) they do not neutralize specific antigen. As the situation stands there is much left to be desired in such an explanation. For instance, what is meant by a "normal" antibody? Is such an antibody inevitably neutralizing, i.e., one which binds antigen so that clinical disease is prevented or cure effected? Such are the antitoxins, blocking antibodies and other neutralizing antibodies generally. The premise that reagins are "abnormal" and are only found in those with an inherited disposition is not correct as reagins are found in a great number of nonatopic human beings when they are exposed to certain agents (ascaris, et cetera).

Schèrago[73] discusses the problem with respect to bacterial allergy and comes to the following conclusions: "Of the five types of bacterial hypersensitiveness, three (anaphylaxis, atopy and heterophile toxicity) do not differ materially from their prototypes to nonbacterial agents. The other two (tuberculin-type and Shwartzman-type) have thus far been induced and elicited only with micro-organisms and their products. It is possible that underlying all types of hypersensitiveness is a common basic principle, namely, that the exposure of the tissues to an undigested foreign or abnormal substance stimulates the production of specific antibody, different for each substance, and that the different forms of hypersensitivity reactions are effects that result from the interaction of antibody and antigen under different conditions." Again, there is much that may be argued pro and con here. Although Scherago considered only hypersensitive states, we miss at least passing mention of antigen-antibody interactions that end in clinical insensitivity. We miss it if only as a realization that these too are common "effects that result from interaction of antibody and antigen under different conditions." Also tuberculin type sensitivities often have been duplicated with nonbacterial substances (Frei, Sulzberger, R. L. Mayer, Landsteiner and Chase, Epstein[26]). The Shwartzman phenomenon on the basis of the definition of allergy previously discussed is a nonallergic event as the alteration in the capacity to react is not *specifically* acquired. We wonder, too, what is meant by "different conditions." Are different shock organs implied? And we doubt that "undigested foreign proteins" or "abnormal substances" can be presumed to evoke just one type of antibody differing only in specificity and in that the reaction type is determined by "different conditions."

An interesting observation is reported by Birkhaug and Böe[10] demonstrating that the induction of an allergic state to BCG and anaphylactic sensitization in guinea pigs with horse serum both produce a restricting influence in the skin to the spread of nonspecific vital dyes. Moreover, specific desensitization of the bacterial allergic state and of the anaphylaxis abolishes the restricting capacity of the skin to the spread of nonspecific vital dyes. The interpretation of this phenomenon is left open but interesting speculation can be made about the nonspecific alterations in physiology that results from allergic states. For example, in recent years the enzyme hyaluronidase has received attention as probably being the "spreading factor."[25] For nearly twenty years it has been known that injection of suspensions of bacteria or India ink together with the "spreading factor of Duran-Reynals" promoted invasion of tissues. Can it be that certain allergic hypersensitive states as anaphylaxis and tuberculin sensitivity inhibit the spreading factor and in this manner produce nonspecific protective, immune effects rather than purely baleful effects?

THE HISTAMINE THEORY OF ALLERGY AND THE SO-CALLED ANTIHISTAMINICS

The original demonstration of the similarity of action between histamine and anaphylactic states has led to an astounding readiness to reason that this substance, or hypothetical H substance, is the basis of allergic hypersensitive states. And

by making the error of equating hypersensitivity with allergy, the tendency has been to regard histamine or H substance as the mediator in allergic reactions in general. Without consistent chemical evidence, histamine or H substance is presumed to be released in reaction-producing amounts as a result of the antigen-antibody interaction or, if released in physiologic amounts, to be accompanied by hypersensitivity to it (allergic or nonallergic?).

While there is some evidence which supports the histamine theory in dermatologic allergic states that are characterized by whealing, the facility with which it has been applied in nonurticarial dermatologic allergic states is to our minds not warranted. Although the presence of histamine in the normal skin has been proved, there is up to this time no evidence that in the nonurticarial forms of dermatologic allergic reactions (eczematous, tuberculin-type, et cetera) histamine is released in abnormal quantities or that the tissues are abnormally sensitive to histamine or, most important, that histamine has the inherent capacity to produce the reactions which are seen clinically. The advent of the so-called antihistaminic agents has led to renewed experimental and theoretical consideration of the role which histamine might possibly play in nonurticarial allergic dermatoses.

R. L. Mayer[56,57] concludes: "antihistaminic substances which are a very important addition to the therapy of allergic diseases also constitute a very useful tool for the study of allergic conditions. Its use enables us to detect the activity of histamine or H-like substance and its role in various allergic diseases. During the investigation it has been shown with the help of this tool, that histamine or H-like substance is not only an important factor in anaphylaxis and allergic manifestations which are closely related to anaphylaxis but also in certain other manifestations which until now have not been associated with histamine. Indeed Pyribenzamine, a substance exhibiting strong and specific antihistaminic properties, exerts a definite activity in experimental dermatitis. This fact suggests that H substance also plays an important role in contact dermatitis thus connecting this disease to anaphylaxis and other allergies of an anaphylactic nature."

Great caution is essential in drawing any conclusions from Mayer's interesting work. There is no challenging Mayer's results proving that Pyribenzamine is effective in partially preventing contact dermatitis under the conditions of his experiment. However, it must be remembered that experimental contact dermatitis in guinea pigs' skin may have an urticarial component similar to the urticarial component in many cases of allergic eczematous dermatitis in man. But the deduction from these observations that histamine or H substance consequently is implicated in the production of allergic eczematous dermatitis is in our opinion not warranted. A paper by Brown[13] reasons the same way in what is termed "emotionally" precipitated urticarial conditions. For, a similar case can be made out to show that other hypothetical substances, not histamine, are basically involved in anaphylaxis for instance because Adrenalin, ephedrine and anesthetics also inhibit or interrupt anaphylaxis. It is universally conceded now that the so-called antihistaminics abate many cases of urticaria. The possibility that this is so because of other properties rather than by interference with the action of histamine has been mentioned by Sulzberger.[83] Leavitt and Code[49] have shown a marked local anesthetic action from Benadryl, and Code recently stated that the antihistaminic action of Benadryl and other antihistaminic drugs appears to be independent from their local anesthetic action.

There have been a huge number of papers, of which we cite a few[23,54,64,67,84] on statistical appraisals of clinical results of exhibition of the "antihistaminics" in various diseases, not all allergic. The sum total of the work published on this subject shows that they are desirable and effective palliative agents in about 75 per cent of cases of acute urticaria, about 50 or more per cent of cases of chronic urticaria, and that they are useful antipruritic agents in a small but significant percentage

of other allergic and nonallergic pruritic dermatoses. From the dermatologic viewpoint the greatest disappointment has been their very limited efficacy in the atopic dermatoses.

ATOPIC DERMATITIS

The role and importance of allergic factors in this disease are often obscure. In many cases we have been unable to discover any evidence implicating allergic factors. The elucidation of the precise mechanism producing atopic dermatitis appears not at hand nor is the hope for new means of therapy any brighter.

Attraction to the psychosomatic explanation[17] for dermatoses of obscure etiology has started all over again since the grim realities of the war years are over. In this field there is a tendency to selfdeluding mysticism and escapist obscurantism. What is the general psychosomatic content of a four-month-old infant with atopic dermatitis, what is that of a six-year-old, an adolescent or young adult with this condition, that distinguishes them from ordinary mortals? How does psychosomatic theory explain the spontaneous abatement of the disease in the large majority of cases in early middle life? Does maturity and insight come naturally at twenty et sequitur? In a large clinic material, ordinary observation of personality revealed no significant differences to the reviewers between persons afflicted with cutaneous atopy and those suffering from any other dermatosis. If anything, the former bear their disabilities with more creditable fortitude than the rest of us.

Hill has written two papers[39,40] which discuss the contradictions between skin test results and the clinical and therapeutic effects of exposure or avoidance of skin test-positive and skin test-negative agents. The dissociation between positive test results and the inefficacy of procedures of avoidance of allergens that are incriminated by test is as distressing to physician as patient.

We have gained the impression that from the viewpoint of the allergist the reasons for the intractable nature of atopic dermatitis are as follows:

1. The number of sensitizations (the number of offending allergens) in some cases may be large and much larger than is indicated by testing, no matter how extensive the testing.

2. The duration of each sensitization may be exceedingly variable, or the level of each sensitivity may be constantly rising and falling. Also, the pattern of sensitization, i.e., the kinds of allergens operative at any one time, fluctuates. For example, one of us (RLB) noted that before the war almost all patients with atopic dermatitis who gave positive scratch test reactions reacted to silk protein, and that during the war and since the war the incidence of such reactions among atopic dermatitis cases fell to zero or close to zero. We attribute this disappearance of silk reactions to the lack of exposure to silk. If this interpretation is correct, then the incidence of silk reactions among our atopic dermatitis patients should increase again with the increasing possibilities of exposure to silk materials.

3. Complete avoidance of all allergens offensive at any given moment is nigh impossible.

As indicated above, the currently available "anti-histaminics" have not significantly changed the therapeutic approach to atopic dermatitis. The direction of environmental control is all the more to be sought if the implications of Simon's work[74] should be confirmed. His studies suggest that persons with atopic tendency may get sensitized to body-own substances (danders) from their fellow human beings, particularly persons *en famille,* and even to themselves! However, Simon has been commendably conservative in his conclusions as to the practical importance of his findings.

There has been a revival of interest[24] in the work of Hansen et al[35,36,37] which suggests that there is a disturbance of fatty acid metabolism in atopic derma-

titis in children. Episodes of clinical activity of the disease have been found to be associated with a low plasma level of unsaturated fatty acids. One possible conclusion is that this circumstance plays a role in producing the disease, and the obvious therapeutic conclusion is to rectify the situation by feeding larger amounts of unsaturated fatty acids. Favorable responses have been reported by the Hansen group. Others[24] have not found the treatment beneficial. The difficulty of administering such an apparently easy treatment is considerable. In a small trial we have noted, as has been noted before, that the feeding of as little as 1 teaspoonful of lard, for instance, induces nausea in a large percentage of cases. If the feeding of saturated fatty acids could be proved to be helpful in good measure, it would pay to experiment with culinary arts and the gastronomics of fat digestion.

Stoesser [75,76] contributed two papers recently on blood lipids and eczema. In the earlier ones he recorded evidence that the course of infantile atopic dermatitis during acute upper respiratory infections shows a relationship with the plasma level of unsaturated fatty acids as determined by iodine number readings on plasma. At the onset of such an intercurrent infection there is improvement in the eczema and this coincides with a flooding of the system by unsaturated fatty acids (high iodine number). Shortly thereafter when the grippal episode ends the eczema worsens as the plasma content of unsaturated fatty acids falls precipitously (low iodine number). In his second communication, Stoesser produced dermatitis in rats on fat-free diets which resulted in low plasma iodine numbers. Cures and higher plasma values followed the addition of unsaturated fatty acids to the diet. When children with atopic dermatitis were fed a soybean preparation of high iodine absorption value, clinical improvement followed together with a rise in plasma iodine number.

Again the question is whether the induced low level of unsaturated fatty acids in the blood is causal of cutaneous exacerbation in atopic dermatitis or whether both events are owing to a common other cause. It would be interesting to see whether severe febrile diseases which are accompanied by improvement in atopic dermatitis (the opposite of the effect of the common cold) are attended by high plasma values for unsaturated fatty acids.

Norrlind[61] published an exhaustive monograph on the effect of acute upper respiratory infections on the course of atopic dermatitis. His studies seem to indicate that sensitization to bacterial antigens is one of the reasons for exacerbations of atopic dermatitis.

ALLERGIC ECZEMATOUS CONTACT-TYPE DERMATITIS

This title is taken from the usage developed by Sulzberger.[78,81] "Allergic" connotes specifically acquired alteration in the capacity to react in the senses detailed above. In this type of allergic state a delayed, or late, fourty-eight-hour response is characteristic. "Eczematous" means a clinical combination of some of the following: edema, papules, vesicles, oozing, thickening, lichenification, scaling or pigmentation. "Contact-type" indicates that the allergen usually reaches the shock tissue (epidermis?) from without (exogenously). This designation does not preclude the possibility (which is frequently enough the case) of allergen approaching from within (endogenously). The telling point is that in either event the clinical gross morphology is eczematous and that the histopathologic picture is that of epidermal spongiosis in the classical manner. These three modifying adjectives serve to classify more exactly one disease entity which is a part of the large group of eczemas and to distinguish this dermatosis from presumably nonallergic eczemas like the mummular, seborrheic, solar, actinic and caloric. It also serves to separate it from other allergic eczemas of vaguer mechanism like the infectious eczemas and eczematoid processes like atopic dermatitis.

Compared to atopic dermatitis, allergic eczematous contact-type dermatitis is a much more satisfying and, at the moment, more rewarding field of study. Often the allergens are simple chemical compounds or plants which are readily identified in a high percentage of cases with reasonable detective ingenuity and effort. Patch testing is an easy and, if properly executed, relatively safe confirmatory routine. Cure by avoidance of the offending agent is frequent and dramatic.

However, the problem basic to all hypersensitive allergic states leading to clinical disease, namely, how to reverse the allergic state, i.e., reconstitute the affected individual to the original insensitive or normergic state, remains. Improvement by hyposensitization procedures, as a lesser goal, is also unsolved in allergic eczematous contact-type dermatitis. Antibodies and antigen-antibody interactions are not convincingly demonstrable as yet on this type of allergic state. Controversy has raged on this point for many years. Some[31] claim to have detected antibodies by means of the classical Prausnitz-Küstner experiment with the sera of persons with allergic eczematous contact-type dermatitis; others[88] and recently again Mom and Ballestero[5] have claimed actual reproduction of the clinical disease by the Urbach-Königstein modification of passive transfer. We[52] have recently performed similar experiments utilizing the Urbach-Königstein technique with completely negative results, and as is well known W. Jadassohn[46] and Sulzberger[79] have never been able to confirm positive findings claimed despite extensive trials. However, further investigations with new techniques and approaches such as those used by Haxthausen[38] may in the future lend further support to the findings of those who claim to have demonstrated passive transfer antibodies in eczematous dermatitis.

Epstein[23] discusses in a general and speculative way, the other forms of skin test reactions that eczematogenic allergens may produce. In particular he notes delayed, tuberculin-type reactions to intradermal introduction of allergens that ordinarily give eczematous responses to patch tests in persons with eczematous sensitizations. He relates this phenomenon to certain drug eruptions which can then be conceived as tuberculin-type responses to eczematogenic allergens with the difference from allergic contact-type eczematous dermatitis being in that the site of shock tissues is somewhat lower than ordinarily in eczematous dermatitis and that clinically the approach of allergen is from within (or experimental deposition is deeper.) It appears possible that the edematous and erythematous appearance of some cases of contact-type dermatitis can be explained on the same basis: the site of shock tissue and reaction being, in part, in the capillaries of the papillae of the upper cutis. This position is fairly readily approached from without as well as from within and can explain the urticarial component of some cases of allergic eczematous contact-type dermatitis (e.g., poison ivy dermatitis). These phenomena can be related, as do Epstein and Rostenberg,[70] to the concept of haptens and it may be that the way or variety of ways in which a given eczematogenic allergen combines with larger molecules at any time determines the form and site, or multiplicity of forms and sites, of allergic sensitization and reaction. It is well substantiated from Landsteiner's work and subsequent clinical check that any of several radicles of a chemical complex may act as determinants of specificity of type or form of allergic transformation.

We find a very minor item to quarrel with in Epstein's article. The use of words like "dermitis" and "epidermitis" are philologically peculiar if not absolutely incorrect. The suffix "-itis" does not inherently mean inflammation and though it may be argued that it has acquired that meaning by force of long usage in that sense, it is still unnecessary to compound it arbitrarily to compete with already adequate and philologically proper words like dermatitis. It would be well to realize that "-itis" is a Greek adjectival ending with the force of "relating to," "deriving from," et cetera. The Greeks spoke of nosos dermatitis (disease of the

skin, skin disease), nosos gastritis, nosos arthritis, et cetera. But as is linguistic habit, the adjective has become a noun with the whole meaning of the phrase and signifying inflammation by secondary attribution. The proper stem with which to form words from derma is dermat-. "Dermitis" and "epidermitis" are philologic monstrosities. An article on related problems of technical philology by one of us (M.L.[53]) is in press. Also it is a moot question whether inflammation can properly be spoken of as occurring in a nonvascular tissue such as the epidermis.

Howell contributed two interesting papers on allergic eczematous contact-type dermatitis. One[44] analysed a fairly large material from private practice which illustrates the great variety of allergenic substances implicated and the high rate of discovery with diligent search. In the other[45] treatment of acute poison ivy dermatitis by injection of "specific" extracts is argued to be theoretically irrational and, more important, shown by clinical trial to be utterly ineffective. Howell also brings simple but the more effective proof that the available commercial extracts vary tremendously in their allergenic potency from one brand to the next and at times from batch to batch of the same brand.

There have appeared several case reports of allergic eczematous contact-type dermatitis which are significant for collateral reasons. Keil, Wasserman and Dawson[47] reported on mango dermatitis and demonstrated cross-sensitizations between the allergenic principles of the mango tree, poison ivy, bhilawanol oil, cashew nut, et cetera. The botanical connection as anacardiaceae is traced and the practical sociologic significance of cross-sensitization is stressed.

The phenomenon of cross-sensitization is receiving more attention at the moment. Very startling and useful facts are being uncovered. For example, Dobkevitch and Baer[21] described contact dermatitis due to the azodyes in nylon stockings and have discovered cross-reactions between paraphenylenediamine and the azodyes commonly used in nylon stockings. The chemical and biologic reasons for such cross-reactions were presented in 1928 by R. L. Mayer. More work is in progress in the same direction by Baer and coworkers on similar cross-reactivity between the above dyes and the azodyes used to color everyday foods, drugs and cosmetics. It is possible that some cases of dermatoses that have been attributed to food sensitivity may turn out to be due to ingested food dyes that evoke allergic eczematous contact-type dermatitis in persons with eczematous sensitization by endogenous approach of the simple chemical allergens.

This leads directly into eczematous dermatitis due to "food allergy" which has had many proponents. Everyone has seen cases which patients claimed were due to the ingestion of particular foods, and many observers have at times accepted such a possibility in certain cases. When a patient claims with great certainty that such and such a food is causative, it has always struck us as peculiar that the eruption is present at all, since, from the very certainty and conviction on the part of the patient of what ails him, one would think the patient would strictly avoid the supposedly offending food and not have the dermatosis. Such, however, is not the case. When a case of urticaria is clearly caused by a food, frequently the patient will know exactly which food, or group of foods, is operative, and clinical testing (not skin testing!) merely confirms, and possibly uncovers, closely related sensitivities. Such patients keep themselves comfortable by avoidance of the obvious and often seek advice only when avoidance is difficult because traces of the food at fault occur in occult manners in other foods or when they seek desensitization because they feel incomplete or imperfect when they cannot ingest, say, kumquats.

The reports by Flood and Perry[28,29] and by Rowe[71] are strongly suggestive of the causal nature of foods in a significant percentage of cases of eczematous dermatitis of the hands. However, much more confirmatory evidence is needed

before the importance of foods in the causation of a significant percentage of eruptions of this type can be definitely accepted. In Rowe's series the long periods of treatment may have been attended by numerous nonspecific beneficial factors. Flood and Perry state that "pyogenic and trichophytic infections are often superimposed on the underlying food sensitivity dermatitis. This must be recognized and eliminated before food testing can be interpreted." One may ask how such superimposed pyogenic and fungous infections can be recognized and eliminated with certainty.

The question of eczematous eruptions of the hands caused by foods is a complex one. Among the factors in foods which may conceivably be the causes of such eruptions are not only the "protein" fraction and the "oil" fraction or some other fraction in the raw materials of the food but also adjuvants such as preservatives (benzoates, saltpeter, et cetera), antimolds (propionic acid, et cetera), dyes (azodyes, et cetera; see above) and agents used in the preparation of the foods (bromates, iodized salt, et cetera). Not only must these and other factors be considered as *ingested* articles but if the food is at all handled by the patient they may also become causal factors by simple *contact* with the hands.

The matter must remain *sub judice*. More clinical observation, histologic studies and patch, scratch and intradermal testing with all the factors listed, are necessary to bring further supportive proof that ingested food (protein) allergens are capable of producing allergic eczematous dermatitis, in addition to the well-recognized usual urticarial and atopic dermatoses.

The same difficulties mentioned in connection with eczematous eruptions of the hands due to foods apply to the findings and conclusions of Rugeley[72] on food allergy as a cause of pruritus ani. That some cases of pruritus ani may be due to food sensitivity had been previously suggested. The only proven case of pruritus ani due to a food which one of us (RLB) has seen was a characteristic allergic eczematous contact-type dermatitis in the perianal area due to mango fruit. In this case there was also dermatitis of the perioral area. Much further investigation of cases of pruritus ani for possible food allergy is necessary before definite conclusions can be drawn from Rugeley's findings.

Sulzberger, Kanof, Baer and Lowenberg[82] report on sensitization to sulfonamides from topical application. They conclude: (1) As regards the incidence of sensitization on topical application, the sulfonamides tested can be arranged in order of increasing sensitizing potential and this order corresponds to increasing solubility in water. The order is sulfadiazine, sulfathiazole, sulfanilamide, sodium sulfadiazine. (2) Cross-sensitization to other related compounds occurs with significant frequency after exposure to a sulfonamide. (3) Preceding more or less superficial skin damage at the site of topical application is a powerful influence in increasing the incidence of sensitization by externally applied sulfonamides. (4) Previous exposure to and/or skin sensitization by externally applied sulfonamides materially increases the risk of cutaneous and general reactions on subsequent oral administration of the same or related drugs.

Another paper by Philips[66] on the same subject contains valuable clinical and test observations.

Hinman[42] counted a 4.5 per cent incidence of eczematous dermatitis in personnel who refinished the stocks of captured Japanese rifles. The high incidence in those known sensitive to poison ivy and poison oak is noteworthy. It is interesting to speculate what was the incidence of contact-dermatitis from this circumstance among Japanese soldiery and what amount of military help our forces received from this windfall of enemy disability.

Rostenberg[69] recounts the occurrence of eczematous sensitization to natural hair of several animals, namely, the coati-mundi, raccoon and skunk. The zoologic relationship is traced. The allergen was found not to be soluble in acetone or ether.

Leider[51] reported what is believed to be the first proved case of epidermal sensitization to DDT. Criteria of proof are fulfilled including a positive patch test with a standardized test material. The fortunately low sensitizing potential of DDT is remarked.

ALLERGY TO ANTIBIOTICS

The number of agents that may induce and elicit an allergic state of eczematous hypersensitivity is legion. Sensitization to simple chemical compounds like the inorganic salts of the heavy metals, e.g., mercury, arsenic and nickel (indeed to the elements themselves!) and to still relatively simple organic agents like paraphenylenediamine, quinine, sulfonamides, et cetera, are old stories. Since the advent of penicillin, eczematous sensitizations to comparatively complex compounds like the crystalline salts of penicillin (but still not of the order of protein) and to what must be similar products of other fungi have attracted attention. Particular interest centers about penicillin because of the variety of cutaneous and general allergic states and allergic reactions it may induce and elicit. The importance of this agent in the management of hitherto hopeless disease or diseases that have up to now always resulted in serious permanent morbidity or disability, has led several perspicacious observers[7,15,18,30,32,41,55,58,60,62,63] to discuss and emphasize its high sensitizing potential. This has become all the more pressing because penicillin seems so harmless on first exhibition and is consequently being used recklessly. It would seem that many types of cutaneous and constitutional allergic states have already been observed to be caused by penicillin. It is obvious then that blithe disregard of future consequences in the use of antibiotics is fraught with danger. For, it may soon come to pass that since the over-all sensitizing potential of penicillin seems to be about 5 per cent and since nearly everybody is receiving the agent for trivial conditions and for diseases where it is utterly ineffective, every 20th person may in the future be denied the use of the agent in serious illness because of previous sensitization. It is to be considered too whether the units of morbidity induced by senseless sensitization may not ultimately begin to outweigh the units of benefit. Such lessons should not only hereafter be kept in mind for penicillin but for the future development of antibiotic therapy. Of other antibiotics that are being used in some volume now, tyrothricin seems to have an extremely low sensitizing capacity. Grolnick[33] reports that tyrothricin is a poor sensitizing agent. The reviewers who have by now had wide experience with the clinical topical use of tyrothricin have never seen a case of allergic sensitization from it. Because of its low sensitizing capacity and its unfitness for systemic use, tyrothricin is the antibiotic of choice for local application in cutaneous infections with micro-organisms which are susceptible to it. Unfortunately, the same does not apply to streptomycin. This agent is not yet extensively employed because it is still very expensive and but recently released from rationed control. M. Strauss[77] and Warring have collected a series of cases of eczematous dermatitis from streptomycin in nurses handling the drug and one of us (M. L) has observed a case of eczematous sensitization from its topical use (1:500 aq. sol) in otitis externa (presumably a pseudomonas aeruginosa infection where it has been reported[14] to be curative). Reuse upon recurrence two months after original topical exhibition resulted in exacerbation of the eczema. Patch test with a solution corresponding in potency to that originally used gave a 4+ eczematous reaction.

This brings up the whole problem of the eczematous forms of the superficial mycoses; it has been observed before[79] that these could be looked upon as allergic eczematous contact-type dermatitis and in principle no different from the condition caused by, say, poison ivy, nail polish or any other eczematogenic allergen. Both dermatophytosis and dermatophytids are eczematous sensitizations to fungi and/or their products. The clinical and histologic appearances of the superficial mycoses,

the affinity of dermatophytes for dead material such as keratin, their lodgement and proliferation in the stratum corneum where they and their products act virtually like a continuous patch test, the similarity to penicillin reactions that are eczematous and which are associated with positive eczematous reactions to patch tests with penicillin—all these points again tend to support the close resemblance of eczematous fungous infections and "ids" and of allergic eczematous contact-type dermatitis. There is some evidence also to indicate a common eczematogenic allergen present in some common dermatotropic fungi and in penicillin.

Cormia and Lewis[19] and Cormia, Lewis and Hopper[20] have studied penicillin sensitization experimentally with special reference to cross-sensitization with trichophytin. Positive evidence of such cross-sensitization was obtained by tuberculin-type reactions and by the Schultz-Dale experiment to both penicillin and trichophytin, no matter which was used as the original.

Peck and Siegal[65] reported a successful hyposensitization to penicillin in a patient who had developed an erythemato-vesicular eruption from the drug. The patient's hypersensitivity was also manifested by a forty-eight-hour delayed tuberculin-type response to intracutaneous test with penicillin. As there is evidence that spontaneous hyposensitization or desensitization occurs in the eczematous and urticarial forms of allergic penicillin hypersensitivity, the possibility cannot be ruled out that the desensitization in the case described by Peck and Siegal may have occurred spontaneously.

MISCELLANY

Sulzberger and Baer[80] and Blum, Baer and Sulzberger[11] studied a case of hypersensitivity to light which manifested itself by urticaria and systemic reactions and showed the presence of Prausnitz-Küstner reagins. This finding, together with a limited effective range of ultra violet radiation ($\lambda < 3700$), permits speculation on the effect of the radiation on tissue (containing proantigen?) resulting in conversion of the proantigen into antigen or in the release of the antigen and thus the evocation of the specific reaction.

In another study the same workers[4] illustrate the effect of Pyribenzamine on dermographism. With a simple technique of standardizing the dermographic stroke by usng equal strips of adhesive tape that were ripped off before and after the exhibition of Pyribenzamine, the inhibiting effect on whealing was demonstrated in a convincing manner. No conclusion about the role of histamine is drawn from the experiment.

The interest in atabrine dermatitis seems to have reached its peak. Extensive clinical descriptions and statistical analyses have appeared.[1,6,8,9,34,90] The exact mechanism of the eruption remains, however, obscure. Not even some of the marks of allergy that commonly obtain for some of the other drug eruptions can always be shown in atabrine dermatitis. The study of these atabrine dermatoses is particularly difficult because exacerbation upon readministration is often lacking. This does not, however, deny an allergic mechanism. It is so easy to imagine prolonged sojourn of the drug *in vivo,* strange hapten conjugation, autosensitization, et cetera, to explain the odd course of this dermatosis.

A revival of interest and speculation about the allergic nature of infectious processes, particularly syphilis, is evident by the appearance of two long papers on the subject. Leider[50] wrote a synthetic account of his conception of the clinical and immunologic events of syphilis against a map of allergic concepts such as are detailed in this review. Urbach and Beerman[87] wrote another account. Perusal of both these papers are recommended as an intellectual exercise and for further speculation and study. The points of difference may briefly be spotted here by quoting from Urbach and Beerman as follows: "Allergy may be defined as the alteration in an organism's capacity to react to a *non-toxic* (our italics) substance

as the result of the production of antibodies. Allergy can therefore express itself either as hypersensitiveness or as hyposensitiveness. Immunity is a state of increased resistance to, or tolerance of, *pathogenic*† agents and/or their products, the change being due to an increase in specific antibodies. Thus according to these definitions, immunity is a special form of allergic hypersensitiveness. In other words, the concept of allergy is more comprehensive; the two terms must not, therefore, be set against each other." While one can agree in a general way with the subcategorization of some forms of immunity under allergy, there is a lack of clarity in the manner the terms "nontoxic," "pathogenic," "hypersensitiveness," "hyposensitiveness," "resistance" and "tolerance" are used.

In consequence of such theoretical points as are discussed in these papers, we noted reports of work by Arnold, Mahoney and Cutler[2,3] on problems of reinfectivity with syphilis in animals after apparent clinical cure with penicillin. Such data will be of the utmost practical and theoretical interest.

REFERENCES

1. Alden, H.S., and Frank, L.J.: Atypical lichenoid dermatitis: a drug eruption due to quinacrine hydrochloride (atabrine). Arch. Dermat. & Syph., 56:13, (July) 1947.
2. Arnold, R.C.; Mahoney, J.F., and Cutler, J.C.: Reinfection in experimental syphilis in rabbits following penicillin therapy. I. Reinfection in early infectious syphilis. Am. J. Syph., Gonor. & Ven. Dis., 31:264, 1947.
3. Arnold, R.C.; Mahoney, J.F., and Cutler, J.C.: Reinfection in experimental syphilis in rabbits following penicillin therapy. II. Reinfection in early latent syphilis. Am. J. Syph., Gonor. & Ven. Dis., 31:489, 1947.
4. Baer, R. L., and Sulzberger, M. B.: Effect of Pyribenzamine on dermographism. J. Invest. Dermat., 7:201, 1946.
5. Ballestero, L.H., and Mom, A.M.: Passive transfer of experimental contact dermatitis with the Urbach-Koenigstein technique. Ann. Allergy, 3:435, 1935.
6. Bazemore, J.J.; Johnson, H.H.; Swanson, E. R., and Hayman, J.M.: Relation of quinacrine hydrochloride to lichenoid dermatitis (atypical lichen planus). Arch. Dermat. & Syph., 54:308, (Sept.) 1946.
7. Bauer, G.H.: Allergic dermatoses complicating penicillin therapy. Arch. Dermat. & Syph., 54:292, (Sept.) 1946.
8. Becker, F. T.: Dermatitis due to quinacrine hydrochloride. Arch. Dermat. & Syph., 54:338, (Sept.) 1946.
9. Bereston, E.S., and Saslaw, N.S.: Complications of lichenoid dermatitis: glomerulonephritis and severe pigmentary changes in the exfoliative stage of lichenoid dermatitis. Arch. Dermat. & Syph., 54:325, (Sept.) 1946.
10. Birkhaug, K., and Böe, Johs: Intradermal spread of vital dye in anaphylaxis and bacterial allergy. J. Immunol., 54:107, (Oct.) 1946.
11. Blum, H.F.; Baer, R.L., and Sulzberger, M.B.: Studies in hypersensitivity to light. II. Urticaria solare ($\lambda <$ 3700). J. Invest. Dermat., 7:99, 1947.
12. Boyd, W.C.: Immunochemistry: A review intended especially for students of allergy. J. Allergy, 18:125, (March) 1947.
13. Brown, W.T.: The probable role of histamine in some emotionally precipitated allergic conditions. Yale J. Biol. & Med., 19:63, (Oct.) 1946.
14. Callaway, J.L.: Pseudomonas aeruginosa infection of the ear treated with streptomycin. Arch. Dermat. & Syph., 55:257, (Feb.) 1947.
15. Chu, W.C., and Cutting, W.C.: Allergic sensitization to penicillin. Experimental results. Proc. Soc. Exper. Biol. & Med., 63:347, (Nov.) 1946.
16. Cooke, R.A.: Allergy in Theory and Practice. Philadelphia: W. B. Saunders Co., 1947.
17. Cormia, F.E.: Psychosomatic factors in dermatoses. Arch. Dermat. & Syph., 55:1, (May) 1947.
18. Cormia, F.E., and Olsener, W.D.: Uses and abuses of penicillin in dermatology Arch. Dermat. & Syph., 54:136, (Aug.) 1946.
19. Cormia, F.E., and Lewis, G.M.: Experimental aspects of penicillin sensitization with special reference to conjoint sensitization to superficial fungus disease. J. Invest. Dermat., 7:375, (Dec.) 1946.

†Our italics.—EDITOR.

20. Cormia, F.E.; Lewis, G.M., and Hopper, M.E.: Experimental aspects of penicillin sensitization with reference to the Schultz-Dale phenomenon. J. Invest. Dermat., 8:395, (June) 1947.
21. Dobkevitch, S., and Baer, R.L.: Cutaneous cross-hypersensitivity to azo-dyes in nylon stockings and to paraphenylenediamine. J. Invest. Dermat., (in press).
22. Doerr, R.R.: The integration and differentiation of allergic phenomena. Ann. Allergy, 4:339, (Sept.-Oct.) 1946.
23. Editorial: Ann. Allergy, 4:400, (Sept.-Oct.) 1946.
24. Editorial: Essential fatty acids and infantile eczema. J.A.M.A., 134:606, (June 14) 1947.
25. Editorial: The biologic significance of hyaluronidase, J.A.M.A., 135:160, (Sept. 20) 1947.
26. Epstein, S.: The role of dermal non-atopic sensitivity (tuberculin-type sensitivity) in contact dermatitis. Ann. Allergy, 4:438, (Nov.-Dec.) 1946.
27. Feinberg, S.M.: Allergy in Practice. Second, revised edition. Chicago: The Year Book Publishers, Inc., 1946.
28. Flood, J.M., and Perry, D.J.: Recurrent vesicular eruption of the hands due to food allergy. J. Invest. Dermat., 7:309, (Dec.) 1946.
29. Flood, J.M., and Perry, D.J.: Role of food allergy in eczematoid dermatitis. Arch. Dermat. & Syph., 55:493, (April) 1947.
30. Friedlander, S; Watrous, R., and Feinberg, S.M.: Contact dermatitis from penicillin: the source of the antigen. Arch. Dermat. & Syph., 54:517, (Nov.) 1946.
31. Cited in Goldsmith, W. N.: Recent Advances in Dermatology. p. 107. Philadelphia: P. Blakiston's Son & Co., 1936.
32. Goodman, H.: Dermatitis due to preparation and administration of penicillin solution. Arch. Dermat. & Syph., 54:206, (Aug.) 1946.
33. Grolnick, M.: Studies to determine the ability of tyrothricin to sensitize the skin. J. Allergy, 17:284, (Sept.) 1946.
34. Grant Peterkin, G.A.: Preliminary report of a dermatosis due possibly to mepacrine. A description of 26 cases seen in Italy. Brit. J. Dermat., 58:263, (Nov.-Dec.) 1946.
35. Hansen, A.E.: Serum lipid changes and therapeutic effects of various oils in infantile eczema. Proc. Soc. Exper. Biol. & Med., 31:160, 1933.
36. Hansen, A. E.: Serum lipids in eczema and in other pathologic conditions. Am. J. Dis. Child, 53:933, (April) 1937.
37. Hansen, A.E.; Knott, E.M.; Wiese, H.F.; Shaperman, E., and McQuarrie, I: Eczema and essential fatty acids. Am. J. Dis. Child., 73:1, (Jan.) 1947.
38. Haxthausen, H.: Studies on the role of the lymphocytes as transmitters of the hypersensitiveness in allergic eczema. Acta Dermat.—Ven., 27:275, 1947.
39. Hill, L.W.: The pathogenesis of infantile eczema. J. Allergy, 18:60, (Jan.) 1946.
40. Hill, L.W.: Some problems of atopic dermatitis in infancy and childhood. J. Allergy, 18:181, (May) 1947.
41. Hinman, A.T.; Warner, G.F., and Li, J.C.: Delayed reactions following penicillin therapy: preliminary report. California Med., 65:112, (Sept.) 1946.
42. Hinman, F.: Contact dermatitis from Japanese rifles. Ann. Allergy, 4:384, (Sept.-Oct.) 1946.
43. Hooker, S.B.: Some properties of antigens and antibodies. Ann. Allergy, 4:425, (Nov.-Dec.) 1946.
44. Howell, J.B.: Contact dermatitis: analysis and tabulation of all cases proved in a single year. Arch. Dermat. & Syph., 53:265, (March) 1946.
45. Howell, J.B.: Evaluation of the intramuscular injections of specific extracts in the treatment of acute poison ivy dermatitis. Ann. Allergy, 5:219, (May-June) 1947.
46. Jadassohn, W.: Die Immunbiologie der Haut. In Jadassohn, J.: Handbuch d. Haut u. Geschlechtskrankheiten. p. 353-478. Berlin: Springer, 1932.
47. Keil, H.; Wasserman, D., and Dawson, C.R.: Mango dermatitis and its relationship to poison ivy sensitivity. Ann. Allergy, 4:268, (July-Aug.) 1946.
48. Landsteiner, K.: The Specificity of Serologic Reactions. Footnote 79, p. 197. Revised edition. Cambridge, Mass.: Harvard University Press, 1945.
49. Leavitt, M.D., and Code, C.F.: Anesthetic action of beta-dimethylaminoethyl benzhydryl ether hydrochloride Benadryl in the skin of human beings. Proc. Soc. Exper. Biol. & Med. 65:33, 1947.
50. Leider, M.: Semantic confusion and resolution in the concepts of cure in syphilis and of reinfection with syphilis. Am. J. of Syph., Gonor. & Ven. Dis., 30:344, (July) 1946.

51. Leider, M.: Allergic eczematous contact-type dermatitis caused by DDT. J. Invest. Dermat., 8:125, (March) 1947.
52. Leider, M., and Baer, R.L.: The present status of passive transfer antibodies in allergic eczematous contact-type dermatitis. Failure to demonstrate passive transfer antibodies. (In preparation).
53. Leider, M., and Rosenblum, M.: A philological note on a certain classical suffix commonly used in dermatologic and general medical nomenclature. J. Invest. Dermat. (In press).
54. Lynch, F.W.: Benadryl in dermatologic therapy. Arch. Dermat. & Syph., 55:101, (Jan.) 1947.
55. MacInnis, K.B.: Allergic reactions from handling penicillin. Ann. Allergy, 5:102, (March-April) 1947.
56. Mayer, R.L.: Anti-histaminic substances in experimental sensitizations. Ann. Allergy, 5:113, (March-April) 1947.
57. Mayer, R.L.: Pyribenzamine in experimental nonallergic and allergic dermatitis. J. Invest. Dermat. 8:67, (Feb.) 1947.
58. Mendell, T.H.: Severe allergic reactions to penicillin. Am. J. M. Sci., 212:541, (Nov.) 1946.
59. Miller, H., and Campbell, D. H.: Reagins: preliminary report on experimental evidence in support of a new theory of their nature. Ann. Allergy, 5:236, (May-June) 1947.
60. Nolan, D. E., and Pedijo, G. W.: Exfoliative dermatitis following penicillin therapy. Ann. Int. Med., 25:725, (Oct.) 1946.
61. Norrlind, R.: Prurigo besnier (atopic dermatitis): clinical experimental study of its pathogenesis with special reference to acute infections of the respiratory tract. Acta Dermat.-Ven., Supp. 13, 26:1-168, 1946.
62. Oberst, F.W., and Murray, M.: Dermatitis from a large dose of penicillin taken orally: report of a case. Arch. Dermat. & Syph., 54:514, (Nov.) 1946.
63. O'Donovan, W.J., and Klorfajn, I.: Sensitivity to penicillin, anaphylaxis and desensitization. Lancet, 2:444, (Sept. 28) 1946.
64. Osborne, E.D.; Jordan, J. W., and Rauch, N.G.: Clinical use of a new antihistaminic compound (Pyribenzamine) in certain cutaneous disorders. Arch. Dermat. & Syph., 55:309, (March) 1947.
65. Peck, S.M., and Siegal, S.H.: Successful desensitization in penicillin sensitivity. J.A.M.A., 134:1546, 1947.
66. Philips, B.: A clinical study of sulfonamide dermatitis. Brit. J. Dermat., 58:213 (Sept.-Oct.) 1946.
67. Pinkus, H.: Benadryl in the treatment of erythema exsudativum multiforme. Ann. Allergy, 4:288, (July-Aug.) 1946.
68. Rich, A.R.: The Pathogenesis of Tuberculosis. Springfield, Ill.: Charles C. Thomas, 1944.
69. Rostenberg, A.: A case of contact dermatitis of eczematous type resulting from sensitization to natural animal hair. J. Allergy, 18:47, (Jan.) 1947.
70. Rostenberg, A.: Eczematous sensitization: a review of its immunologic properties and some speculations as to its nature. Arch. Dermat. & Syph., 56:224, (Aug.) 1947.
71. Rowe, A.H.: Atopic dermatitis of the hands due to food allergy. Arch. Dermat. & Syph., 54:683, (Dec.) 1946.
72. Rugeley, F.R.: Allergic causes of pruritus ani. Ann. Allergy, 4:374, (Sept.-Oct.) 1946.
73. Scherago, M.: Bacterial allergy. Ann. Allergy, 5:1, (Jan.-Feb.) 1947.
74. Simon, F.A.: Atopic dermatitis in infants, children and adults: with special reference to the role of inhalants and dander. J. Allergy, 18:186, (May) 1946.
75. Stoesser, A.V.: Influence of acute infections on the plasma lipids and the course of eczema. J. Allergy, 13:248, 1942.
76. Stoesser, A. V.: The influence of soybean products on the iodine number of plasma lipids and the course of eczema. J. Allergy, 18:29, (Jan.) 1947.
77. Strauss, M.J., and Warring, F.C.: Contact dermatitis from streptomycin. J. Invest. Dermat., 9:3, 1947.
78. Sulzberger, M.B.: Contact-type eczematous dermatitis: modern classification and remarks on therapy. J. Allergy, 18:176, (May) 1947.
79. Sulzberger, M. B.: Dermatologic Allergy. Springfield, Ill.: Charles B. Thomas, 1940.
80. Sulzberger, M.B., and Baer, R.L.: Studies in hypersensitivity to light. J. Invest. Dermat., 6:343, (Dec.) 1945.
81. Sulzberger, M.B.; Baer, R.L., and associates: Office Immunology, Including Allergy. Chicago: The Year Book Publishers, Inc., 1947.

82. Sulzberger, M.B.; Kanof, A.; Baer, R.L., and Lowenberg, C.: Sensitization by topical application of sulfonamides. J. Allergy, 18:92, (March) 1947.
83. Sulzberger, M.B.: Discussion on Mayer, R.L.: Pyribenzamine in nonallergic and allergic dermatitis. J. Invest. Dermat., 8:67, (Feb.) 1947.
84. Todd, L. C.: Some clinical observations on the use of Benadryl for the symptomatic relief of allergic conditions. Ann. Allergy, 4:282, (July-Aug.) 1946.
85. Topley and Wilson's Principles of Bacteriology and Immunity. Third edition. Revised by G.S. Wilson and A.A. Miles. Baltimore: The Williams & Wilkins Company, 1946.
86. Tuft, L.: Clinical Allergy. Philadelphia: W. B. Saunders Co., 1937.
87. Urbach, E., and Beerman, H.: Allergy and immunity in syphilis. Am. J. Syph., Gonor. & Ven. Dis., (March) 1947.
88. Cited in Urbach, E., and Gottlieb, P.M.: Allergy. Second edition, p. 153ff. New York: Grune and Stratton, 1946.
89. von Pirquet, C.: Allergy. München. Med. Wchnschr., 30:1457, 1906. Also to be found in translation into English by M.B. Sulzberger[79] and by Stephan Epstein in Ann. Allergy, 4:388, (Sept.-Oct.) 1946.
90. Wilson, D.J.: Eczematous and pigmentary lichenoid dermatitis: atypical lichen planus; preliminary report. Arch. Dermat. & Syph., 54:377, (Oct.) 1946.

ANTI-ASTHMATIC EFFECTS OF A NEW SYNTHETIC ANTISPASMODIC

(Continued from Page 540)

vertigo or dizziness in a minority of cases; this is minimized or abolished by proper dosage control.

The following objective criteria for the relief of asthma were employed: disappearance or marked diminution of rhonchi; relief of dyspnea with shortening of the phase of expiration; increase in vital capacity. Subjective criteria were: diminution or disappearance of wheezing, shortness of breath and coughing; ability to sleep horizontally after previous orthopnea; enjoyment of nights of rest after previously consistently disturbed nights. Eighty per cent of moderately severe but still ambulatory asthmatic patients benefited from the use of the drug. During these investigations a definite effort was made to exclude that 25 per cent of asthmatic patients who admit or claim temporary benefit of some degree from any medication, however inert.

REFERENCES

1. Burtner, R. R., and Cusic, J. W.: Antispasmodics. II Basic esters of some polynuclear carboxylic acids. J. Am. Chem. Soc., 65:1582, 1943.
2. Hartman, M. M.: Ethyl-nor-epinephrine by inhalation for bronchial asthma; a comparison with epinephrine. J. Allergy, 17:106, 1946.
3. Kemp, R. S.: Personal communication, (Aug. 30) 1945.
4. Lehmann, G., and Knoefel, P. K.: The spasmolytic and local anesthetic action of some derivatives of fluorene-carboxylic acid and related compounds. J. Pharmacol. & Exper. Therap., 74:274, (March) 1942.
5. Lehmann, G., and Knoefel, P. K.: The spasmolytic and local anesthetic action of some esters of 9,10-dihydroanthracene-carboxylic acid and related compounds. J. Pharmacol. & Exper. Therap., 80:335, (April) 1944.
6. Raymond, A. L.: Recent developments in synthetic antispasmodics. J. Am. Pharm. A., (Scientific Edition) 32:249, (Oct.) 1943.

450 Sutter Street,
San Francisco, California.

News Items

FOURTH ANNUAL MEETING OF THE AMERICAN COLLEGE OF ALLERGISTS

Hotel Pennsylvania, New York City
March 12, 13 and 14, 1948

(Important Notice. All Members Please Read Carefully)

This session promises to be an outstanding success. Both members and non-members are urged to attend. All members and other allergists on our mailing list will be receiving a room reservation card for the Hotel Pennsylvania early in January. If anyone is missed, please write to the Secretary-Treasurer, 423 LaSalle Medical Building, Minneapolis 2, Minnesota, for your card. Fill in these cards and mail them immediately, as all reservations must be made directly with the hotel by those attending the meeting.

Both members and non-members are required to register and receive a badge. The registration desk will open Thursday afternoon, March 11, at 2:00 P.M. Fellows and Associate Fellows must present their membership cards at the desk. There will be no charge for registration.

A meeting of the Board of Directors will be held Thursday morning, March 11, from 9:00 to 10:00, and a meeting of the members of the Board of Regents and ex-officio members only will follow from 10:00 to 12:00. At 2:00 P.M. Thursday, the various committees will meet; namely, the Standardization Committee in conjunction with the Sub-Committee for Certification of Allergenic Extract, New and Unused Therapeutics Committee, and the Committee on the Extension of Postgraduate Education in conjunction with the Sub-Committee on Publications. There will be a meeting of the American Society for the Certification of Allergists on Friday evening at 7:30.

Morning scientific sessions will begin at 9:00 and extend until 1:00 P.M. The afternoon sessions will be held from 2:00 to 5:30. On Saturday afternoon the program will be conducted from 2:00 to 4:00 P. M., and will be followed by the business meeting for all members at 4:15. The cocktail hour, beginning at 6:30, immediately precedes the annual informal banquet in the Georgian Room.

At the time this news item was sent to press, the Program Committee announced a symposium on three topics, focusing upon certain important aspects of allergy. Controversial subjects about which a good deal is known are usually presented. They are: (1) Mold Allergy; (2) Rhinolaryngological Allergy; and (3) Neuro-Allergy.

It is of special importance to note that the third topic, Neuro-Allergy, will be the subject of intensive research during the coming year. It is with a good deal of pleasure, therefore, that the College announces specific plans for the presentation of scientific developments along this line.

The Program Committee urges all Fellows and Associate Fellows who plan to submit papers for consideration to do so before February 1, so that they may be published in the program booklet which will be mailed about ten days before the annual session. All papers should be sent in duplicate, 250 words in length abstracted. Papers may also be presented *by title*. There is no limit to the papers *by title* which anyone can submit and be assured of their publication in the ANNALS, if accepted. However, only one paper of this type from each author may be presented at the meeting. All papers presented *by title* will appear as part of the regular program,

thus assuring the author priority. Abstracts of the papers presented *by title* will be published in the ANNALS, with the papers which are actually given at the meeting. Presenting a paper *by title* does not obligate the author to attend the meeting.

It is too early to present the completed program. However, some of the topics which will be presented are as follows:

"Transmission of Nervous Impulse"—OTTO LOEWI, M.D.

"Clinical Significance of Acetylcholine"—JOSEPH G. HOPKINS, M.D.

"A New Antihistaminic Compound for the Treatment of Urticaria and Hay Fever"—SALVATORE N. SALETTA, M.D.

"Aerosol Penicillin in Allergic Patients with Respiratory Infections"—MAYER A. GREEN, M.D.

"A Durhan Type of Pollen-Collecting Chamber for Sixty-seven Cents"—BERNARD DICKSTEIN, M.D.

"Vulva Pruritus Associated with Hay Fever"—WILLIAM F. MITCHELL, M.D.

"Correlation of Experimental Data with Clinical Behavior of a Group of Synthetic Antihistamine Drugs"—ALEX S. FRIEDLAENDER, M.D., and SIDNEY FRIEDLAENDER, M.D.

"Histamine-Sympathin Balance"—FRANCISCO J. FARRERONS, M.D.

"Behavior of the Normal Histamine of the Rabbit toward Antihistaminic Substances"—FRANCISCO J. FARRERONS, M.D.

"Chronic Urticaria—An Etiological Survey of 125 Cases"—GEORGE L. WALDBOTT, M.D., and GEORE L. SPRINKLE, M.D.

"The Rh Factor in Immunological Reactions"—ALEXANDER S. WIENER, M.D.

"A Clinical Evaluation of a New Antihistaminic Drug Antistine"—MORRIS KAPLAN, M.D., and NORMAN J. EHRLICH, M.D.

"Anaphylactic Shock in Mice"—PHILIP D. MCMASTER, M.D.

"Bacteriologic Studies in Multiple Sclerosis"—EDWARD C. ROSENOW, M.D., and BAYARD T. HORTON, M.D.

"Retrobulbar Neuritis: Treatment with Histamine"—HENRY P. WAGENER, M.D., and BAYARD T. HORTON, M.D.

"Neurological Allergies and Histamine"—HINTON D. JONEZ, M.D.

"Immediate Urticarial Reactions to Intrademral Injections of Bacterial Antigens"—BENNETT KRAFT, M.D., MARK H. MOTHERSILL, M.D., and R. H. NESTMANN, M.D.

"The Electroencephalogram of Allergic Children"—SUSAN C. DEES, M.D., and HANS LOWENBACH, M.D.

"Antitoxin Studies on Refined Tetanus and Diphtheria Toxoids in Allergic Children"—H. G. RAPAPORT, M.D., and M. MURRAY PESHKIN, M.D.

"Comparison of the Antihistaminic Action of Pyribenzamine and Epinephrine in the Human Skin"—H. A. ABRAMSON, M.D., and S. GROSBERG, M.D.

"Clinical Evaluation of a New Antihistamine Drug; 2-Dimethylaminoethoxy-Phenyl-Methyl-2-Picoline Succinate (Decapryn)"—ETHAN ALLAN BROWN, M.D.

"Studies on Acute Disseminated Encephalomyelitis in Rhesus Monkeys"—ELVIN A. KABAT, M.D., ABNER WOLF, M.D., and ADA E. BEZER, M.D.

POST CONVENTION PLEASURE TRIP

An official trip to Bermuda has been arranged for any of those attending the Fourth Annual Session of the American College of Allergists at the Hotel Pennsylvania, New York City, March 12-14, 1948. Arrangements have been made with the Travel Shop, 105 South Fifth Street, Minneapolis, to handle all details, without charge, at official transportation and hotel rates. Plans are being made for leaving New York on Monday morning, March 15, by a mammoth, luxurious Pan American Clipper and arriving in sunny Bermuda just three hours later. The round-trip air fare, New York to Bermuda, is $144.90, U. S. tax included. First class hotel accommodations will be provided in Bermuda at rates ranging from $12 per day with meals.

When making reservations for this official post-convention trip, please state the names in full of those in your party desiring to go, together with their age, sex, nationality, and the number of days your party desires to stay in Bermuda. A deposit of $100 for each person making reservations should be enclosed. Do not miss this opportunity by delaying! Limited plane space and hotel accommodations make early reservations necessary.

CINCINNATI INSTRUCTIONAL COURSE

One of the largest and most successful instructional courses in allergy ever to be held was recently conducted by the College under the auspices of the College of Medicine, University of Cincinnati, November 3-8, inclusive. There were forty-three instructors, the majority from the teaching staffs of leading universities in the United States. The total registration of physicians attending this course, exclusive of the faculty, was 169. Dr. George E. Rockwell was chairman and director of the committee.

THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

The thirty-second annual meeting of the American Association of Immunologists will be held with the Federation of American Societies for Experimental Biology in Atlantic City, March 15 and 16, 1948. The date of the usual joint meeting with the American Society for Experimental Pathology will probably be March 16.

The Federation headquarters will be at the Chalfonte-Haddon Hall.

SOUTHWEST ALLERGY FORUM

We are pleased to announce that the next meeting of the Southwest Allergy Forum will be held on April 5 and 6, 1948, at the Biltmore Hotel, Oklahoma City, Oklahoma. The Executive Committee of this Society is composed of: Dr. Herbert J. Rinkel, president, Kansas City, Mo.; Dr. Sim Hulsey, president-elect, Fort Worth, Texas; Dr. Fannie L. Leney, secretary-treasurer, Oklahoma City, Okla.; Dr. Carrol Pounders, Oklahoma City, Okla.; Dr. Nesbeitt Miller, Oklahoma City, Oklahoma.

CENTRAL PENNSYLVANIA ALLERGY SOCIETY

The recent meeting of the Central Pennsylvania Allergy Society was attended by nearly one hundred and fifty members. Dr. Stephen Lockey of Lancaster, Dr. Harvey Simmons of Harrisburg, and Dr. Ralph M. Mulligan of Reading, were re-elected to the offices of president, vice president, and secretary-treasurer, respectively, for the year 1948. The next meeting will be held in York, in April, 1948, with Dr. Arthur Kalisch as chairman of arrangements.

The following men were elected to membership: Dr. Walter Werley, Reading; Dr. Paul Craig, Reading; Dr. Archibald Judd, Hamburg; Dr. Z. Estes, Lancaster; Dr. J. Welch, Lancaster; Dr. J. D. Diehl, West Chester; Dr. Lester Lowle, Lewisburg; Dr. Nelson Scharadin, Cleona; Dr. B. H. Hamner, Williamsport; Dr. Harry Mullin, Scranton; Dr. Luther King, Meadville; Dr. Wilfred Langley, Sayre; Dr. Charles Koniver, Allentown.

* * *

Harry L. Rogers, M.D., announces the removal of his office to 1537 Pine Street, Philadelphia, Pa.

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112 diagnostic *Allergens*

FOOD ALLERGENS

Almond
Apple
Apricot
Asparagus
Banana
Barley
Bean
Beef
Beet
Brazil Nut
Broccoli
Buckwheat
Cabbage
Cantaloupe
Carrot
Cauliflower
Celery
Cheese, American
Cheese, Swiss
Cherry
Chicken
Clam, Hard
Cocoa
Cocoanut
Codfish
Coffee
Corn
Crab
Cucumber
Duck
Eggwhite
Eggyolk
Flounder
Gelatin
Ginger
Grape (Raisin)
Grapefruit
Halibut
Herring
Honeydew
Lactalbumin
Lamb
Lettuce
Lima Bean
Lobster
Mackerel
Milk (Cow)
Mushroom
Mustard
Oat
Onion
Orange
Oyster
Pea
Peanut
Pecan
Pepper (Red, Green)
Perch
Pike
Pineapple
Pork
Potato
Prune (Plum)
Pumpkin
Quince Seed
Radish
Rice
Rye
Salmon
Sardine
Scallop
Shrimp
Soy Bean
Spinach
Strawberry
Sweet Potato
Tomato
Tuna Fish
Veal
Walnut (English)
Wheat
Whitefish (Lake)
Yeast

INCIDENTAL ALLERGENS

Cotton Seed
Dust
Flaxseed
Glue
Gum Karaya
Kapok
Orris Root
Pyrethrum
Silk
Tobacco

EPIDERMAL ALLERGENS

Cat Hair
Cattle Hair
Dog Hair
Goat Hair
Feathers, mixed
Hog Hair
Horse Dander
Rabbit Hair
Sheep Wool

FUNGUS ALLERGENS

Alternaria sp.
Aspergillus fumigatus
Chaetomium sp.
Cladosporium
Epidermophyton inguinale
Hormodendron
Monilia sitophila
Mucor plumbeus
Penicillium digitatum
Trichophyton interdigitale

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Pabena *8 oz. packages*	A new form of Pablum, in which the only cereal grain is oatmeal. Has essentially the same nutritional advantages of Pablum, and all of its convenient and economical points.
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Mead's Standardized Cod Liver Oil *4 oz., 8 oz. and 16 oz. bottles*	Each gram supplies not less than 1,800 vitamin A units and 175 vitamin D units (U.S.P.).
Mead's Viosterol in Oil *10 c.c. and 50 c.c. bottles*	For disturbances of calcium-phosphorus metabolism. Supplies 10,000 U.S.P. vitamin D units per gram.
Mead's Cod Liver Oil with Viosterol *4 oz. and 16 oz. bottles*	Contains 1,800 vitamin A units and 400 vitamin D units (U.S.P.) per gram.
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Mead's Halibut Liver Oil *10 c.c. and 50 c.c. bottles*	For vitamin A therapy. Each gram supplies 60,000 vitamin A units and 850 vitamin D units (U.S.P.)
Mead's Brewers Yeast Tablets *Bottles of 250 and 1,000 tablets*	For deficiencies of vitamin B complex. Each tablet contains not less than 0.06 mg. thiamine, 0.02 mg. riboflavin and 0.15 mg. niacin.
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